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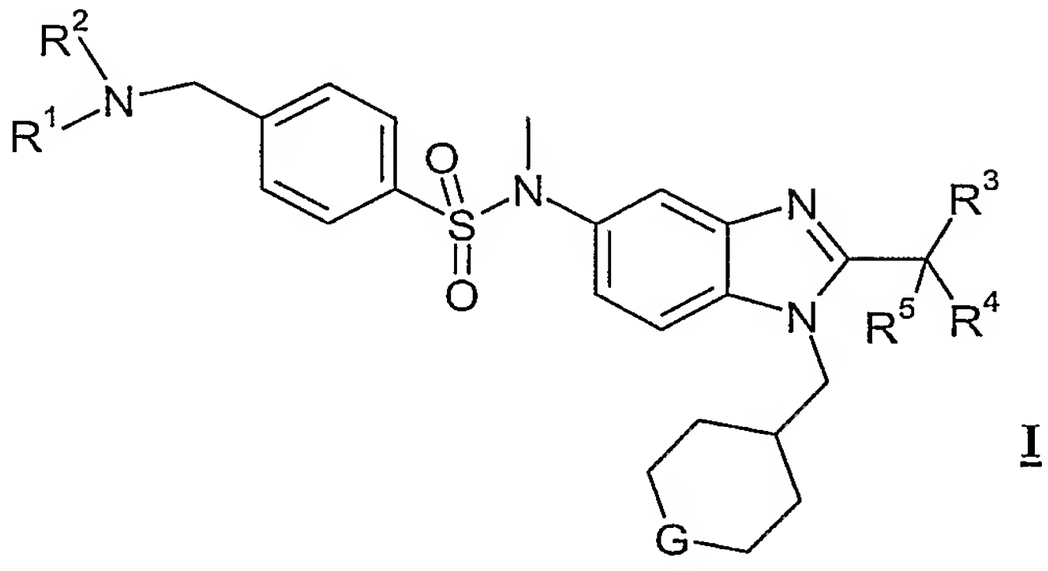


I

(57) Abstract: Compounds of Formula I, or pharmaceutically acceptable salts thereof (I) wherein G, R^1, R^2, R^3, R^4, and R^5 are as defined in the specification as well as salts and pharmaceutical compositions including the compounds are prepared. They are useful in therapy, in particular in the management of pain.

WO 2006/033627 A1

COMPOUNDS, COMPOSITIONS CONTAINING THEM, PREPARATION THEREOF AND USES THEREOF IIII

BACKGROUND OF THE INVENTION

1. Field of the invention

The invention is related to therapeutic compounds, pharmaceutical compositions containing these compounds, manufacturing processes thereof and uses thereof. Particularly, the present invention is related to compounds that may be effective in treating pain, cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and/or cardiovascular disorders.

2. Discussion of Relevant Technology

Pain management has been studied for many years. It is known that cannabinoid receptor (e.g., CB_1 receptor, CB_2 receptor) ligands including agonists, antagonists and inverse agonists produce relief of pain in a variety of animal models by interacting with CB_1 and/or CB_2 receptors. Generally, CB_1 receptors are located predominantly in the central nervous system, whereas CB_2 receptors are located primarily in the periphery and are primarily restricted to the cells and tissues derived from the immune system.

While CB_1 receptor agonists, such as Δ^9-tetrahydrocannabinol (Δ^9-THC) and anadamide, are useful in anti-nociception models in animals, they tend to exert undesired CNS side-effects, e.g., psychoactive side effects, the abuse potential, drug dependence and tolerance, etc. These undesired side effects are known to be mediated by the CB_1 receptors located in CNS. There are lines of evidence, however, suggesting that CB_1 agonists acting at peripheral sites or with limited CNS exposure can manage pain in humans or animals with much improved overall in vivo profile.

Therefore, there is a need for new CB_1 receptor ligands such as agonists that may be useful in managing pain or treating other related symptoms or diseases with reduced or minimal undesirable CNS side-effects.

DESCRIPTION OF THE EMBODIMENTS

The present invention provides CB_1 receptor ligands which may be useful in treating pain and/or other related symptoms or diseases.

The term "C_{m-n}" or "C_{m-n} group" used alone or as a prefix, refers to any group having m to n carbon atoms.

The term "alkyl" used alone or as a suffix or prefix, refers to a saturated monovalent straight or branched chain hydrocarbon radical comprising 1 to about 12 carbon atoms. Illustrative examples of alkyls include, but are not limited to, C_{1-4}alkyl groups, such as methyl, ethyl, propyl, isopropyl, 2-methyl-1-propyl, 2-methyl-2-propyl, butyl, isobutyl, t-butyl.

The term "cycloalkyl," used alone or as suffix or prefix, refers to a saturated monovalent ring-containing hydrocarbon radical comprising at least 3 up to about 12 carbon atoms. Examples of cycloalkyls include, but are not limited to, C_{3-7}cycloalkyl groups, such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl, and saturated cyclic and bicyclic terpenes. A cycloalkyl can be unsubstituted or substituted by one or two suitable substituents. Preferably, the cycloalkyl is a monocyclic ring or bicyclic ring.

The term "alkoxy" used alone or as a suffix or prefix, refers to radicals of the general formula –O-R, wherein R is an alkyl. Exemplary alkoxy includes methoxy, ethoxy, propoxy, isopropoxy, butoxy, t-butoxy, and isobutoxy.

The term "heterocycle" used alone or as a suffix or prefix, refers to a ring-containing structure or molecule having one or more multivalent heteroatoms, independently selected from N, O, P and S, as a part of the ring structure and including at least 3 and up to about 20 atoms in the ring(s). Heterocycle may be saturated or unsaturated, containing one or more double bonds, and heterocycle may contain more than one ring. When a heterocycle contains more than one ring, the rings may be fused or unfused. Fused rings generally refer to at least two rings sharing two atoms therebetween. Heterocycle may have aromatic character or may not have aromatic character.

Heterocycle includes, for example, monocyclic heterocycles such as: aziridine, oxirane, thiirane, azetidine, oxetane, thietane, pyrrolidine, pyrroline, imidazolidine, pyrazolidine, pyrazoline, dioxolane, sulfolane 2,3-dihydrofuran, 2,5-

dihydrofuran tetrahydrofuran, thiophane, piperidine, 1,2,3,6-tetrahydro-pyridine, piperazine, morpholine, thiomorpholine, pyran, thiopyran, 2,3-dihydropyran, tetrahydropyran, 1,4-dihydropyridine, 1,4-dioxane, 1,3-dioxane, dioxane, homopiperidine, 2,3,4,7-tetrahydro-1*H*-azepine homopiperazine, 1,3-dioxepane, 4,7-dihydro-1,3-dioxepin, and hexamethylene oxide.

In addition, heterocycle includes aromatic heterocycles, for example, pyridine, pyrazine, pyrimidine, pyridazine, thiophene, furan, furazan, pyrrole, imidazole, thiazole, oxazole, pyrazole, isothiazole, isoxazole, 1,2,3-triazole, tetrazole, 1,2,3-thiadiazole, 1,2,3-oxadiazole, 1,2,4-triazole, 1,2,4-thiadiazole, 1,2,4-oxadiazole, 1,3,4-triazole, 1,3,4-thiadiazole, and 1,3,4- oxadiazole.

Additionally, heterocycle encompass polycyclic heterocycles, for example, indole, indoline, isoindoline, quinoline, tetrahydroquinoline, isoquinoline, tetrahydroisoquinoline, 1,4-benzodioxan, coumarin, dihydrocoumarin, benzofuran, 2,3-dihydrobenzofuran, isobenzofuran, chromene, chroman, isochroman, xanthene, phenoxathiin, thianthrene, indolizine, isoindole, indazole, purine, phthalazine, naphthyridine, quinoxaline, quinazoline, cinnoline, pteridine, phenanthridine, perimidine, phenanthroline, phenazine, phenothiazine, phenoxazine, 1,2-benzisoxazole, benzothiophene, benzoxazole, benzthiazole, benzimidazole, benztriazole, thioxanthine, carbazole, carboline, acridine, pyrolizidine, and quinolizidine.

In addition to the polycyclic heterocycles described above, heterocycle includes polycyclic heterocycles wherein the ring fusion between two or more rings includes more than one bond common to both rings and more than two atoms common to both rings. Examples of such bridged heterocycles include quinuclidine, diazabicyclo[2.2.1]heptane and 7-oxabicyclo[2.2.1]heptane.

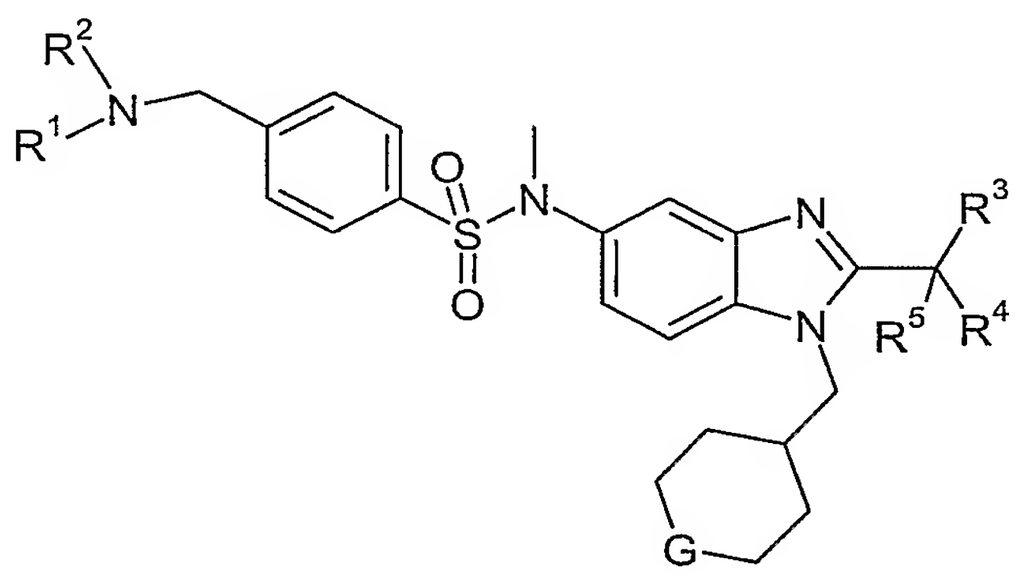
The term "heterocylcoalkyl" used alone or as a suffix or prefix, refers to a monocyclic or polycyclic ring comprising carbon and hydrogen atoms and at least one heteroatom, preferably, 1 to 3 heteroatoms selected from nitrogen, oxygen, and sulfur, and having no unsaturation. Examples of heterocycloalkyl groups include pyrrolidinyl, pyrrolidino, piperidinyl, piperidino, piperazinyl, piperazino, morpholinyl, morpholino, thiomorpholinyl, thiomorpholino, and pyranyl. A heterocycloalkyl group can be unsubstituted or substituted with one or two suitable

substituents. Preferably, the heterocycloalkyl group is a monocyclic or bicyclic ring, more preferably, a monocyclic ring, wherein the ring comprises from 2 to 5 carbon atoms and from 1 to 3 heteroatoms, referred to herein as C_{2-5}heterocycloalkyl.

Halogen includes fluorine, chlorine, bromine and iodine.

"RT" or "rt" means room temperature.

In one aspect, an embodiment of the invention provides a compound of Formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

G is selected from –O-, -CHF- and $–CF_2$-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, and C_{1-4}alkoxy; or R^1 and R^2 together with the N to which they are bound may form a C_{3-6}heterocycle; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

In another embodiment, the compounds may be those of formula I, wherein

G is selected from –O- and $–CF_2$-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, and C_{1-4}alkoxy; or R^1 and R^2 together with the N to which they are bound may form a C_{3-6}heterocycle; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

Another embodiment of the invention provides a compound of formula I, wherein

G is selected from –O- and $–CF_2$-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl, and hydroxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl; or R^1 and R^2 together with the N to which they are bound may form a C_{2-5}heterocycloalkyl; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

A further embodiment of the invention provides a compound of formula I, wherein

G is –O-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl and hydroxy-C_{1-4}alkyl, and C_{1-4}alkoxy-C_{1-4}alkyl with R^1 and R^2 being different groups; or R^1 and R^2 together with the N to which they are bound may form a group selected from 2-oxopyrrolidin-1-yl, pyrrolidin-1-yl, 1*H*-1,2,3-triazol-1-yl, and morpholinyl group; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl with R^3, R^4 and R^5 being the same.

An even further embodiment of the invention provides a compound of formula I,

wherein

G is $–CF_2$-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl and hydroxy-C_{1-4}alkyl, and C_{1-4}alkoxy-C_{1-4}alkyl with R^1 and R^2 being different groups; and

R^3, R^4 and R^5 are each independently methyl.

A further embodiment of the invention provides a compound selected from

N-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylmethyl)benzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(1*H*-1,2,3-triazol-1-ylmethyl)benzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-[(methylamino)methyl]benzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-[(ethylamino)methyl]-*N*-methylbenzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-{[(2-methoxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(pyrrolidin-1-ylmethyl)benzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-[(2-oxopyrrolidin-1-yl)methyl]benzenesulfonamide;

N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide;

and pharmaceutically acceptable salts thereof.

It will be understood that when compounds of the present invention contain one or more chiral centers, the compounds of the invention may exist in, and be isolated as, enantiomeric or diastereomeric forms, or as a racemic mixture. The present invention includes any possible enantiomers, diastereomers, racemates or mixtures thereof, of a compound of Formula I. The optically active forms of the compound of the invention may be prepared, for example, by chiral chromatographic separation of a racemate, by synthesis from optically active starting materials or by asymmetric synthesis based on the procedures described thereafter.

It will also be appreciated that certain compounds of the present invention may exist as geometrical isomers, for example E and Z isomers of alkenes. The present invention includes any geometrical isomer of a compound of Formula I. It will further be understood that the present invention encompasses tautomers of the compounds of the Formula I.

It will also be understood that certain compounds of the present invention may exist in solvated, for example hydrated, as well as unsolvated forms. It will further be understood that the present invention encompasses all such solvated forms of the compounds of the Formula I.

Within the scope of the invention are also salts of the compounds of the Formula I. Generally, pharmaceutically acceptable salts of compounds of the present

invention may be obtained using standard procedures well known in the art, for example by reacting a sufficiently basic compound, for example an alkyl amine with a suitable acid, for example, HCl or acetic acid, to afford a physiologically acceptable anion. It may also be possible to make a corresponding alkali metal (such as sodium, potassium, or lithium) or an alkaline earth metal (such as a calcium) salt by treating a compound of the present invention having a suitably acidic proton, such as a carboxylic acid or a phenol with one equivalent of an alkali metal or alkaline earth metal hydroxide or alkoxide (such as the ethoxide or methoxide), or a suitably basic organic amine (such as choline or meglumine) in an aqueous medium, followed by conventional purification techniques.

In one embodiment, the compound of Formula I above may be converted to a pharmaceutically acceptable salt or solvate thereof, particularly, an acid addition salt such as a hydrochloride, hydrobromide, phosphate, acetate, fumarate, maleate, tartrate, citrate, methanesulphonate or *p*-toluenesulphonate.

We have now found that the compounds of the invention have activity as pharmaceuticals, in particular as modulators or ligands such as agonists, partial agonists, inverse agonist or antagonists of CB_1 receptors. More particularly, the compounds of the invention exhibit selective activity as agonists of the CB_1 receptors and are useful in therapy, especially for relief of various pain conditions such as chronic pain, neuropathic pain, acute pain, cancer pain, pain caused by rheumatoid arthritis, migraine, visceral pain etc. This list should however not be interpreted as exhaustive. Additionally, compounds of the present invention are useful in other disease states in which dysfunction of CB_1 receptors is present or implicated. Furthermore, the compounds of the invention may be used to treat cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, anxiety disorders, gastrointestinal disorders and cardiovascular disorders.

Compounds of the invention are useful as immunomodulators, especially for autoimmune diseases, such as arthritis, for skin grafts, organ transplants and similar surgical needs, for collagen diseases, various allergies, for use as anti-tumour agents and anti viral agents.

Compounds of the invention are useful in disease states where degeneration or dysfunction of cannabinoid receptors is present or implicated in that paradigm. This

may involve the use of isotopically labelled versions of the compounds of the invention in diagnostic techniques and imaging applications such as positron emission tomography (PET).

Compounds of the invention are useful for the treatment of diarrhoea, depression, anxiety and stress-related disorders such as post-traumatic stress disorders, panic disorder, generalized anxiety disorder, social phobia, and obsessive compulsive disorder, urinary incontinence, premature ejaculation, various mental illnesses, cough, lung oedema, various gastro-intestinal disorders, e.g. constipation, functional gastrointestinal disorders such as Irritable Bowel Syndrome and Functional Dyspepsia, Parkinson´s disease and other motor disorders, traumatic brain injury, stroke, cardioprotection following miocardial infarction, spinal injury and drug addiction, including the treatment of alcohol, nicotine, opioid and other drug abuse and for disorders of the sympathetic nervous system for example hypertension.

Compounds of the invention are useful as an analgesic agent for use during general anaesthesia and monitored anaesthesia care. Combinations of agents with different properties are often used to achieve a balance of effects needed to maintain the anaesthetic state (e.g. amnesia, analgesia, muscle relaxation and sedation). Included in this combination are inhaled anaesthetics, hypnotics, anxiolytics, neuromuscular blockers and opioids.

Also within the scope of the invention is the use of any of the compounds according to the Formula I above, for the manufacture of a medicament for the treatment of any of the conditions discussed above.

A further aspect of the invention is a method for the treatment of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such treatment.

Thus, the invention provides a compound of Formula I or pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined for use in therapy.

In a further aspect, the present invention provides the use of a compound of Formula I or a pharmaceutically acceptable salt or solvate thereof, as hereinbefore defined in the manufacture of a medicament for use in therapy.

In the context of the present specification, the term "therapy" also includes "prophylaxis" unless there are specific indications to the contrary. The term "therapeutic" and "therapeutically" should be construed accordingly. The term "therapy" within the context of the present invention further encompasses to administer an effective amount of a compound of the present invention, to mitigate either a pre-existing disease state, acute or chronic, or a recurring condition. This definition also encompasses prophylactic therapies for prevention of recurring conditions and continued therapy for chronic disorders.

The compounds of the present invention are useful in therapy, especially for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

In use for therapy in a warm-blooded animal such as a human, the compound of the invention may be administered in the form of a conventional pharmaceutical composition by any route including orally, intramuscularly, subcutaneously, topically, intranasally, intraperitoneally, intrathoracially, intravenously, epidurally, intrathecally, transdermally, intracerebroventricularly and by injection into the joints.

In one embodiment of the invention, the route of administration may be oral, intravenous or intramuscular.

The dosage will depend on the route of administration, the severity of the disease, age and weight of the patient and other factors normally considered by the attending physician, when determining the individual regimen and dosage level at the most appropriate for a particular patient.

For preparing pharmaceutical compositions from the compounds of this invention, inert, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, dispersible granules, capsules, cachets, and suppositories.

A solid carrier can be one or more substances, which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, or tablet disintegrating agents; it can also be an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided compound of the invention, or the active component. In tablets, the

active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

For preparing suppository compositions, a low-melting wax such as a mixture of fatty acid glycerides and cocoa butter is first melted and the active ingredient is dispersed therein by, for example, stirring. The molten homogeneous mixture in then poured into convenient sized moulds and allowed to cool and solidify.

Suitable carriers are magnesium carbonate, magnesium stearate, talc, lactose, sugar, pectin, dextrin, starch, tragacanth, methyl cellulose, sodium carboxymethyl cellulose, a low-melting wax, cocoa butter, and the like.

The term composition is also intended to include the formulation of the active component with encapsulating material as a carrier providing a capsule in which the active component (with or without other carriers) is surrounded by a carrier which is thus in association with it. Similarly, cachets are included.

Tablets, powders, cachets, and capsules can be used as solid dosage forms suitable for oral administration.

Liquid form compositions include solutions, suspensions, and emulsions. For example, sterile water or water propylene glycol solutions of the active compounds may be liquid preparations suitable for parenteral administration. Liquid compositions can also be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions for oral administration can be prepared by dissolving the active component in water and adding suitable colorants, flavoring agents, stabilizers, and thickening agents as desired. Aqueous suspensions for oral use can be made by dispersing the finely divided active component in water together with a viscous material such as natural synthetic gums, resins, methyl cellulose, sodium carboxymethyl cellulose, and other suspending agents known to the pharmaceutical formulation art.

Depending on the mode of administration, the pharmaceutical composition will preferably include from 0.05% to 99%w (per cent by weight), more preferably from 0.10 to 50%w, of the compound of the invention, all percentages by weight being based on total composition.

A therapeutically effective amount for the practice of the present invention may be determined, by the use of known criteria including the age, weight and response of the individual patient, and interpreted within the context of the disease which is being treated or which is being prevented, by one of ordinary skills in the art.

Within the scope of the invention is the use of any compound of Formula I as defined above for the manufacture of a medicament.

Also within the scope of the invention is the use of any compound of Formula I for the manufacture of a medicament for the therapy of pain.

Additionally provided is the use of any compound according to Formula I for the manufacture of a medicament for the therapy of various pain conditions including, but not limited to: acute pain, chronic pain, neuropathic pain, back pain, cancer pain, and visceral pain.

A further aspect of the invention is a method for therapy of a subject suffering from any of the conditions discussed above, whereby an effective amount of a compound according to the Formula I above, is administered to a patient in need of such therapy.

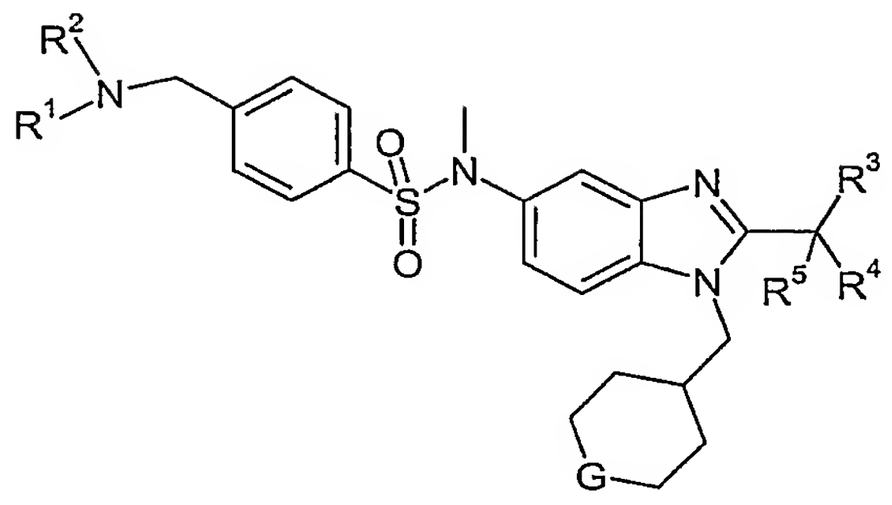
Additionally, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier.

Particularly, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier for therapy, more particularly for therapy of pain.

Further, there is provided a pharmaceutical composition comprising a compound of Formula I or a pharmaceutically acceptable salt thereof, in association with a pharmaceutically acceptable carrier use in any of the conditions discussed above.

In a further aspect, the present invention provides a method of preparing the compounds of the present invention.

In one embodiment, the invention provides a process for preparing a compound of Formula I, comprising:



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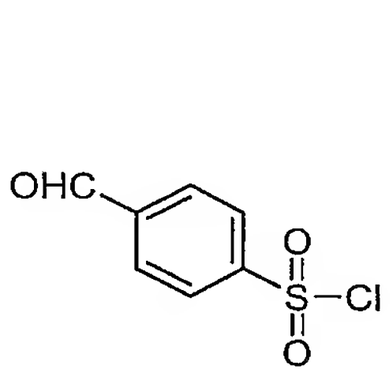
reacting a compound of Formula II with a compound of formula III,



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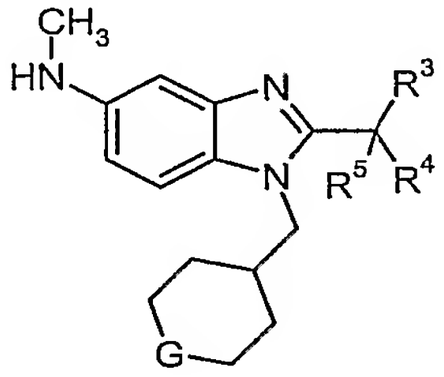
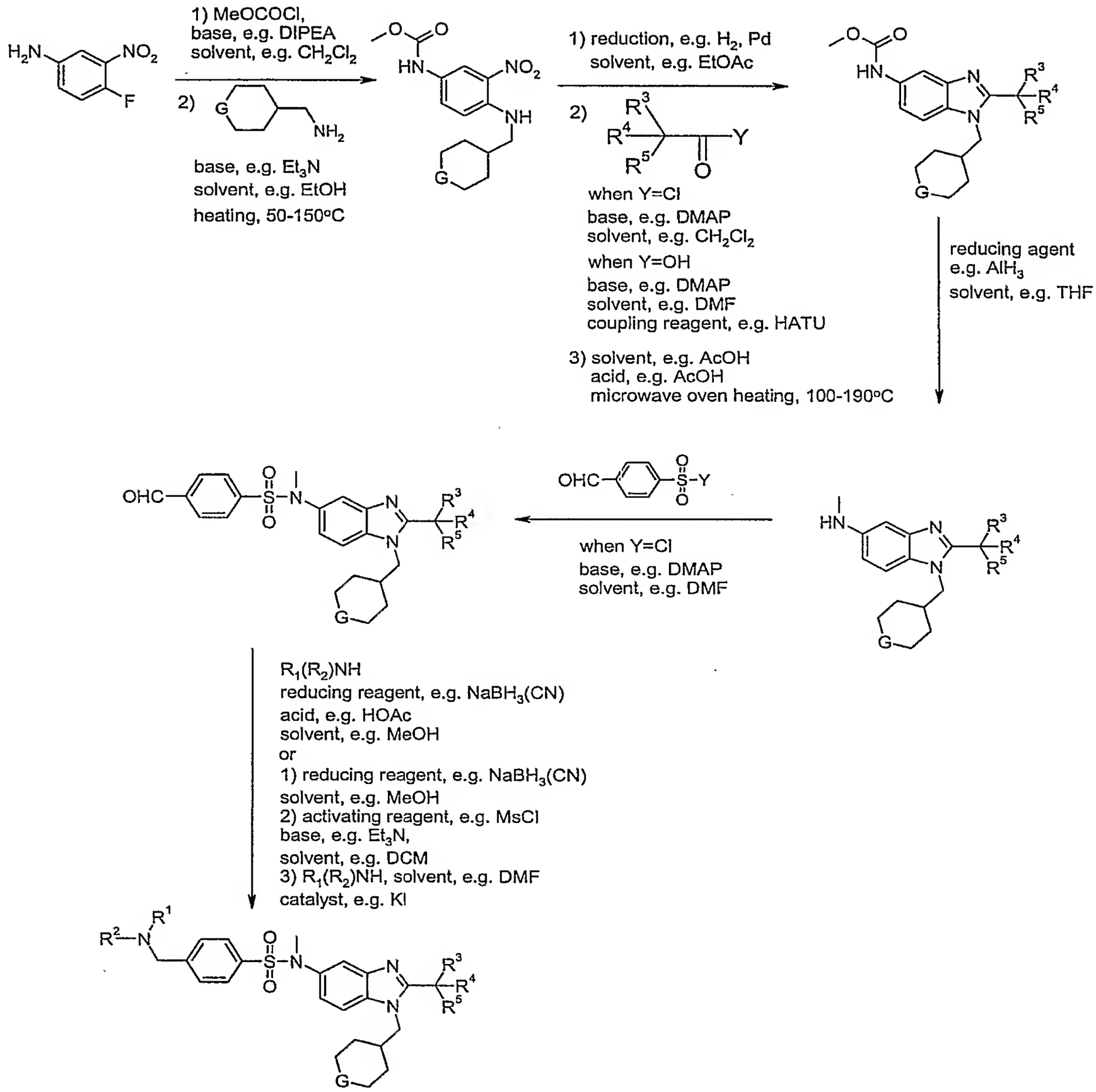


III

followed by reductive amination with $R^1(R^2)NH$ in the presence of a reducing reagent, such as $Na(CN)BH_3$, wherein G, R^1, R^2, R^3, R^4 and R^5 are as defined above. Further, a compound of formula I may be prepared by reacting a compound of Formula II with a compound III followed by a sequence of reactions including 1) reduction with a reducing agent , such as $Na(CN)BH_3$, 2) methanesulfonylation and 3) nucleophilic substitution with $R^1(R^2)NH$, wherein G, R^1, R^2, R^3, R^4 and R^5 are as defined above.

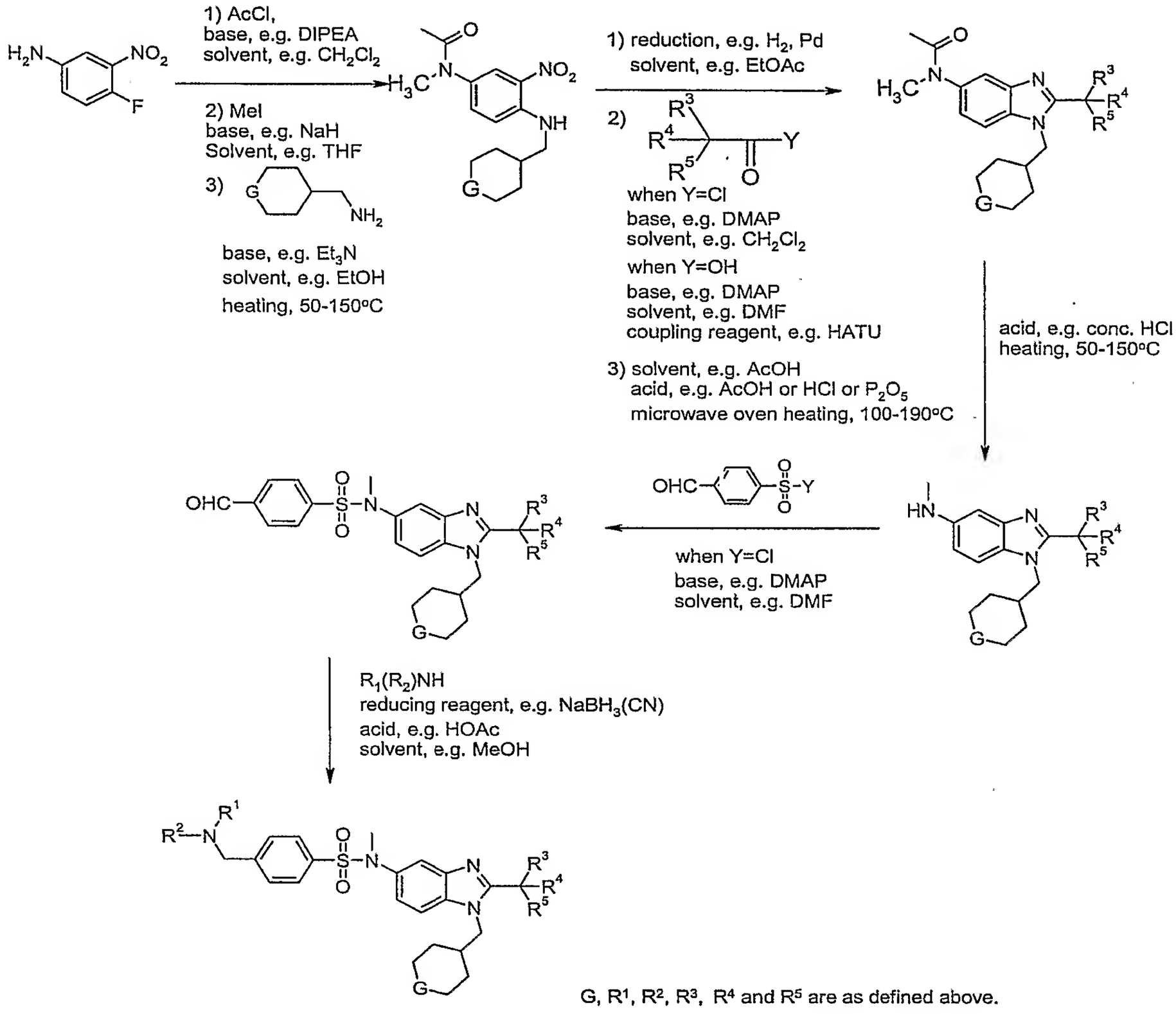
Compounds of the present invention may also be prepared according to the synthetic routes as depicted in Schemes 1, 2 and 3.

Scheme 1



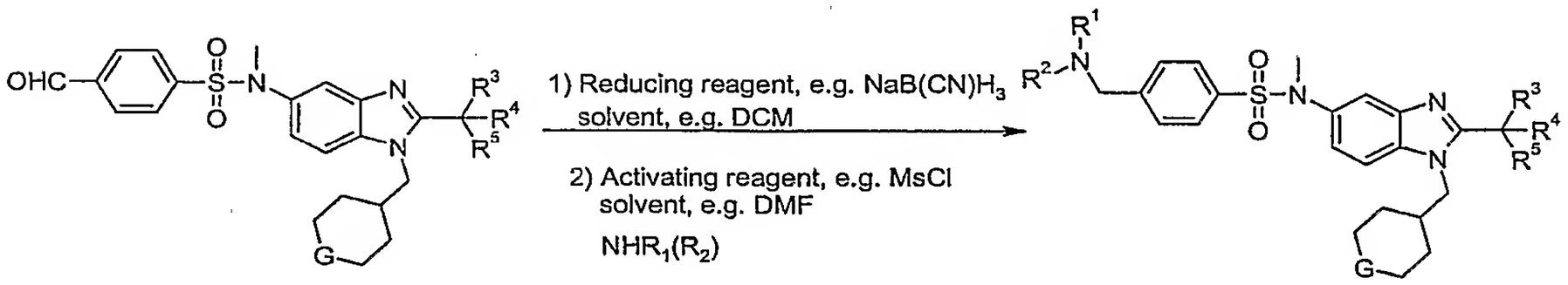
G, R^1, R^2, R^3, R^4 and R^5 are as defined above.

Scheme 2



G, R^1, R^2, R^3, R^4 and R^5 are as defined above.

Scheme 3



G, R^1, R^2, R^3, R^4 and R^5 are as defined above.

Biological Evaluation

hCB_1 and hCB_2 receptor binding

Human CB_1 receptor from Receptor Biology (hCB_1) or human CB_2 receptor from BioSignal (hCB_2) membranes are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle, diluted in the cannabinoid binding buffer (50 mM Tris, 2.5 mM EDTA, 5 mM $MgCl_2$, and 0.5 mg/mL BSA fatty acid free, pH 7.4) and aliquots containing the appropriate amount of protein are distributed in 96-well plates. The IC_{50} of the compounds of the invention at hCB_1 and hCB_2 are evaluated from 10-point dose-response curves done with ^{3}H-CP55,940 at 20000 to 25000 dpm per well (0.17-0.21 nM) in a final volume of 300 µl. The total and non-specific binding are determined in the absence and presence of 0.2 µM of HU210 respectively. The plates are vortexed and incubated for 60 minutes at room temperature, filtered through Unifilters GF/B (presoaked in 0.1% polyethyleneimine) with the Tomtec or Packard harvester using 3 mL of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 0.5 mg BSA pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid.

<u>hCB_1 and hCB_2 GTPγS binding</u>

Human CB_1 receptor from Receptor Biology (hCB_1) or human CB_2 receptor membranes (BioSignal) are thawed at 37 °C, passed 3 times through a 25-gauge blunt-end needle and diluted in the GTPγS binding buffer (50 mM Hepes, 20 mM NaOH, 100 mM NaCl, 1 mM EDTA, 5 mM $MgCl_2$, pH 7.4, 0.1% BSA). The EC_{50} and E_{max} of the compounds of the invention are evaluated from 10-point dose-response curves done in 300µl with the appropriate amount of membrane protein and 100000-130000 dpm of GTPg^{35}S per well (0.11 –0.14 nM). The basal and maximal stimulated binding is determined in absence and presence of 1 µM (hCB_2) or 10 µM (hCB_1) Win 55,212-2 respectively. The membranes are pre-incubated for 5 minutes with 56.25 µM (hCB2) or 112.5 µM (hCB_1) GDP prior to distribution in plates (15 µM (hCB_2) or 30 µM (hCB_1) GDP final). The plates are vortexed and incubated for 60 minutes at room temperature, filtered on Unifilters GF/B (presoaked in water) with the Tomtec or Packard harvester using 3 ml of wash buffer (50 mM Tris, 5 mM $MgCl_2$, 50 mM NaCl, pH 7.0). The filters are dried for 1 hour at 55 °C. The radioactivity (cpm) is counted in a TopCount (Packard) after adding 65 µl/well of MS-20 scintillation liquid. Antagonist reversal studies are done in the same way

except that (a) an agonist dose-response curve is done in the presence of a constant concentration of antagonist, or (b) an antagonist dose-response curve is done in the presence of a constant concentration of agonist.

Based on the above assays, the dissociation constant (Ki) for a particular compound of the invention towards a particular receptor is determined using the following equation:

$Ki = IC_{50}/(1+[rad]/Kd)$,

Wherein IC_{50} is the concentration of the compound of the invention at which 50% displacement has been observed;

[rad] is a standard or reference radioactive ligand concentration at that moment; and

Kd is the dissociation constant of the radioactive ligand towards the particular receptor.

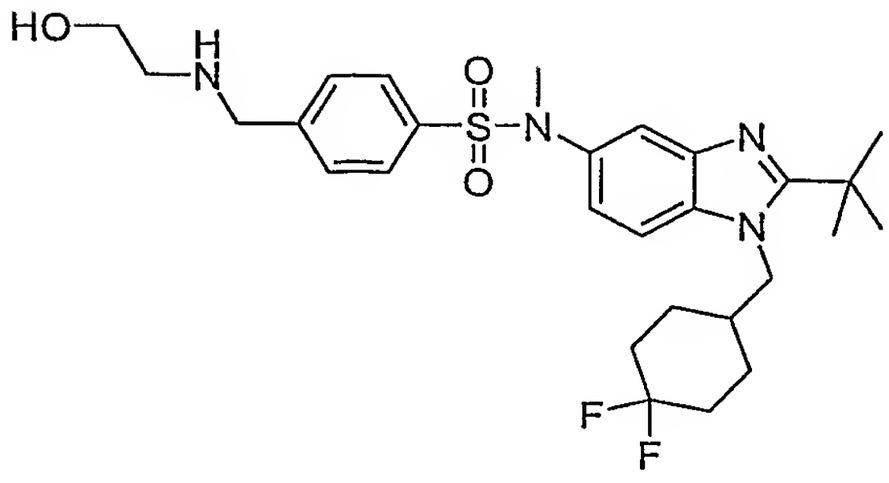
Using the above-mentioned assays, the Ki towards human CB_1 receptors for certain compounds of the invention are in the range of between 8 nM and 1175 nM. EC_{50} for these compounds are in the range of between 12 nM and 49 nM. Emax for these compounds are in the range of between 109% and 143%.

EXAMPLES

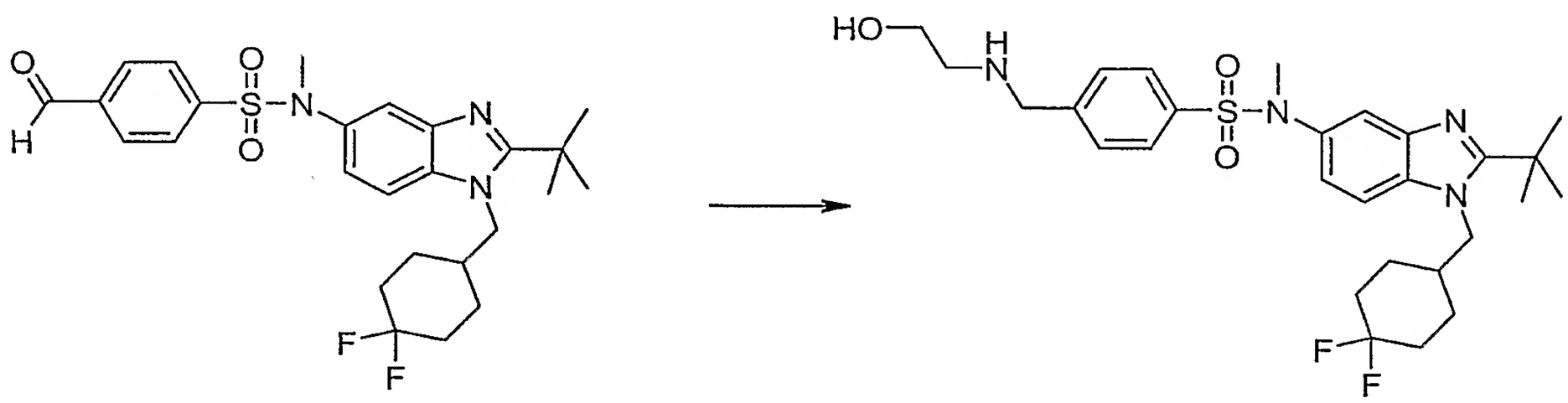
The invention will further be described in more detail by the following Examples which describe methods whereby compounds of the present invention may be prepared, purified, analyzed and biologically tested, and which are not to be construed as limiting the invention.

Example 1

***N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide**

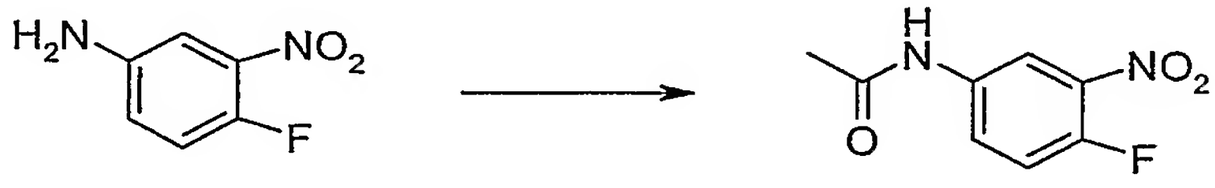


Step A. ***N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide**



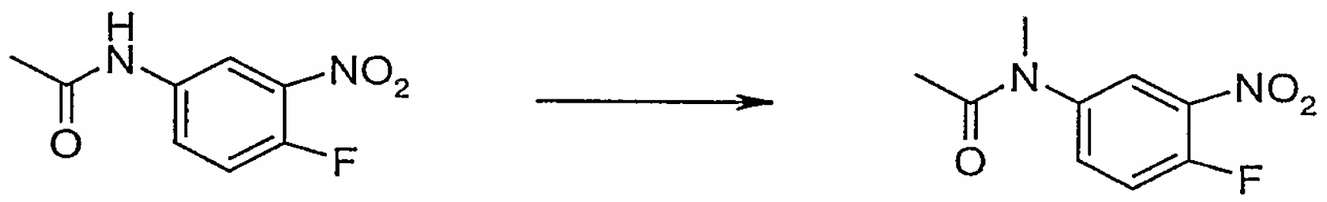
N-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4-formyl-*N*-methylbenzenesulfonamide (1.21 g, 2.40 mmol) (for synthesis, see Steps B to H), 2-ethanolamine (1.45 mL, 24.0 mmol) and AcOH (2 drops) were stirred together in MeOH (15 mL) at room temperature for 1 hr. $NaBH_3CN$ (453 mg, 7.22 mmol) was added and the reaction mixture was stirred for 3 hrs. The solvent was removed and the crude product was purified by preparative reverse-phase HPLC to give the title compound as the corresponding TFA salt. Yield: 950 mg (73%); MS (ESI) $(M+H)^+$: 515.2; ^1H NMR (600 MHz, CD_3OD) δ 1.52 - 1.60 (m, 4 H), 1.67 (s, 9 H), 1.69 - 1.79 (m, 4 H), 2.04 - 2.10 (m, 1 H), 3.15 - 3.19 (m, 2 H), 3.28 (s, 3 H), 3.80 - 3.84 (m, 2 H), 4.34 (s, 2 H), 4.53 (d, J=7.42 Hz, 2 H), 7.29 (dd, J=8.96, 2.05 Hz, 1 H), 7.58 (d, J=1.79 Hz, 1 H), 7.64 - 7.69 (m, 4 H), 7.84 (d, J=9.22 Hz, 1 H).

Step B. ***N*-(4-fluoro-3-nitrophenyl)acetamide**



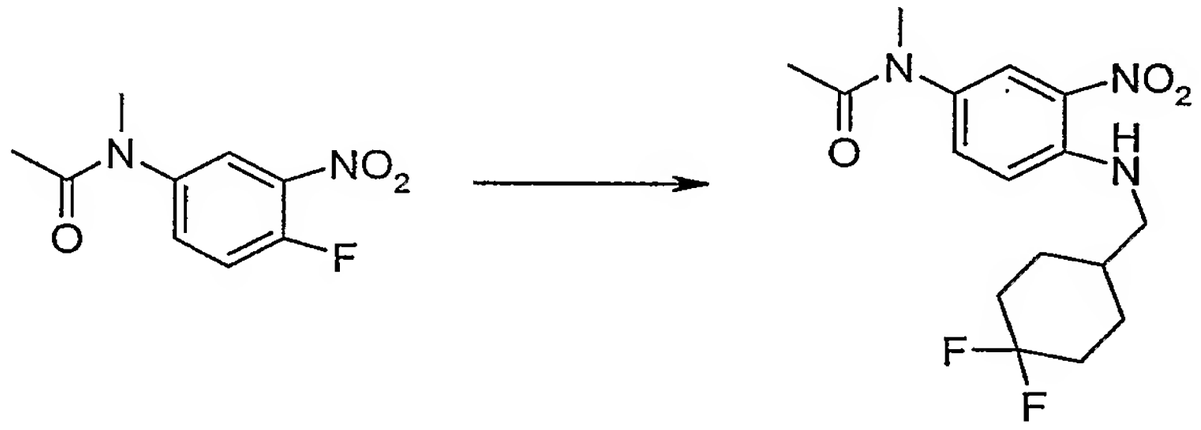
4-Fluoro-3-nitro-aniline (45.0 g, 0.288 mol) was added in portions to acetic anhydride (150 mL) at room temperature. The reaction mixture was stirred at room temperature for 2 h. The white solid was collected and dried *in vacuo* to give the title compound (42.0 g, 70%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.23 (s, 3 H), 7.26 (m, 1 H), 7.50 (s broad, 1 H), 7.87 (m, 1 H), 8.23 (dd, *J*=6.44, 2.73 Hz, 1 H).

Step C. *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide



Sodium hydride (2.40 g, 60 mmol) was added in portions to a solution of *N*-(4-fluoro-3-nitrophenyl)acetamide (7.93 g, 40 mmol) in THF (120 mL) at 0 °C. Stirring for 20 min, iodomethane (17.0 g, 120 mmol) was added. The reaction mixture was stirred at room temperature for 2 h, quenched with saturaed $NaHCO_3$ (30 mL) and extracted with EtOAc (3x100 mL). The combined organic phases were washed with saturated NaCl (2x30 mL). After filtration and concentration, 8.73 g (100%) of the title compound was obtained as a brown solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92 (s, 3 H), 3.30 (s, 3 H), 7.38 (s, 1 H), 7.52 (s, 1 H), 7.95 (s, 1 H).

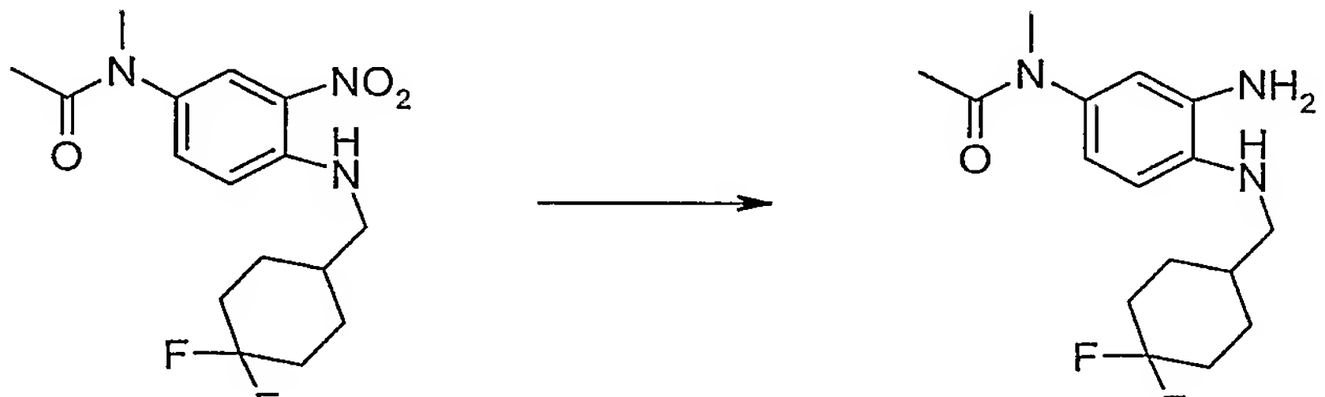
Step D. *N*-(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)-*N*-methylacetamide



[(4,4-difluorocyclohexyl)methyl]amine TFA salt (780 mg, 2.96 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (628 mg, 2.96 mmol) and DIPEA (1.29 mL, 7.40 mmol) in EtOH (15 mL) at room temperature. The reaction mixture was heated for 18 hrs at 70 °C. Following removal of the solvent, the crude

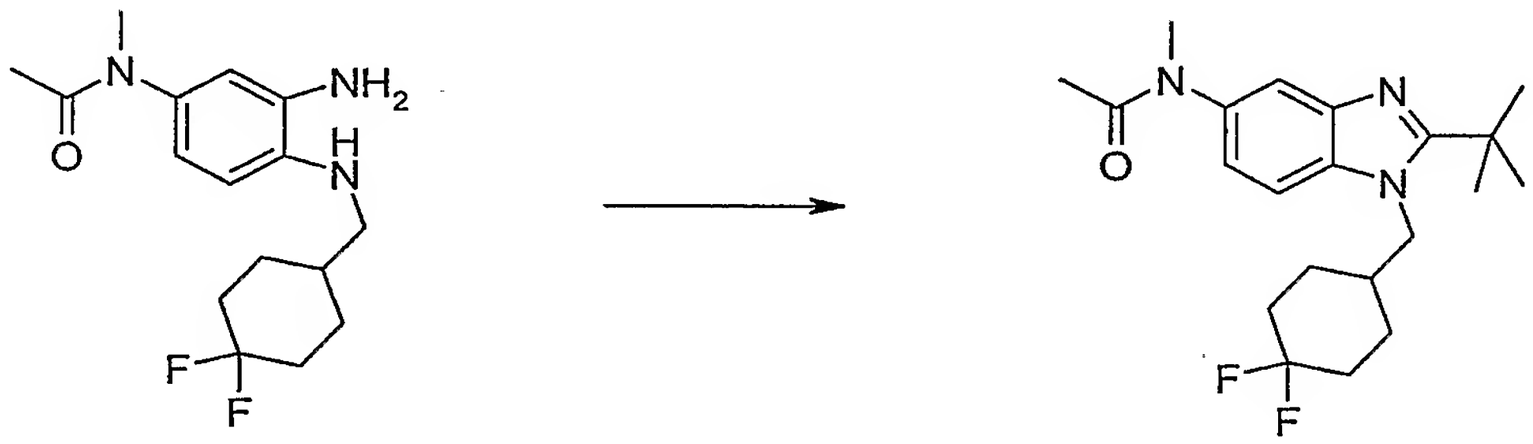
product was purified by MPLC using EtOAc/Heptane 70-100% to give 855 mg (85%) of the title compound as an orange-red solid (84%). MS (ESI) $(M+H)^+$: 341.96.

Step E. *N*-(3-amino-4-{[(4,4-difluorocyclohexyl)methyl]amino}phenyl)-*N*-methylacetamide



N-(4-{[(4,4-difluorocyclohexyl)methyl]amino}-3-nitrophenyl)-*N*-methylacetamide (855 mg, 2.50 mmol) was hydrogenated in ethyl acetate (50 mL) catalyzed by 10% Pd/C at 50 psi H_2 in Parr shaker for 18 h at room temperature. After filtration through celite and concentration, 716 mg (92%) of a white solid was obtained, which was used in the next step without further purification. MS (ESI) $(M+H)^+$: 311.99

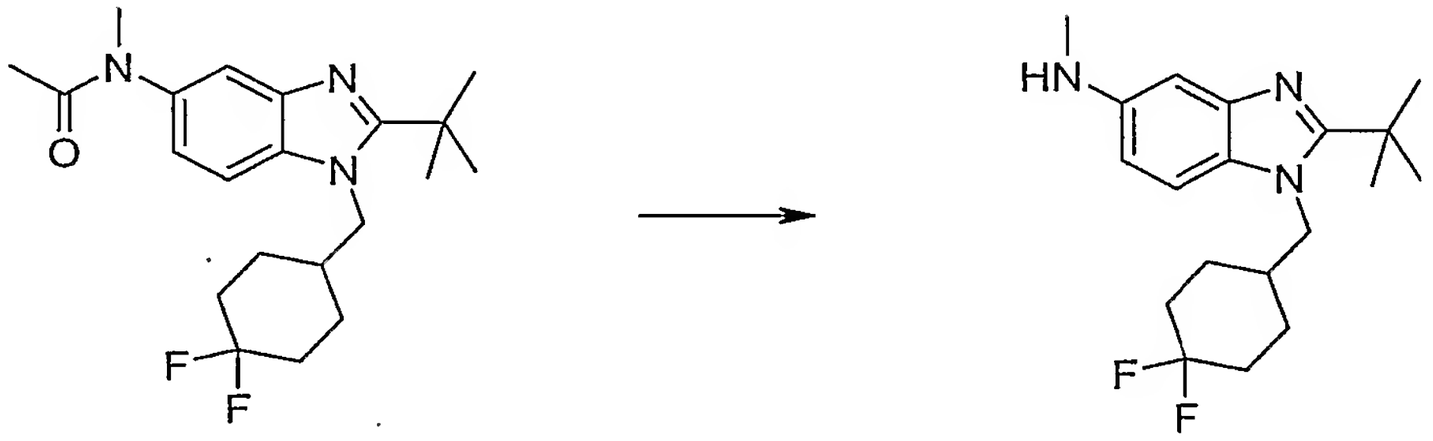
Step F. *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylacetamide



Trimethylacetyl chloride (0.29 mL, 2.41 mmol) was dropwise added to a solution of *N*-(3-amino-4-{[(4,4-difluorocyclohexyl)methyl]amino}phenyl)-*N*-methylacetamide (716 mg, 2.30 mmol) and Et_3N (0.38 mL, 2.75 mmol) in dichloromethane (100 mL) at 0 °C. The resulting mixture was stirred for 4h at room temperature. After evaporation of the solvent, the residue was dissolved in acetic acid (16 mL) and then divided to 4 sealed test tubes. The mixture was heated at 150°C in a Personal Chemistry SmithSynthesizer microwave instrument for 3 hrs. The combined reaction mixture

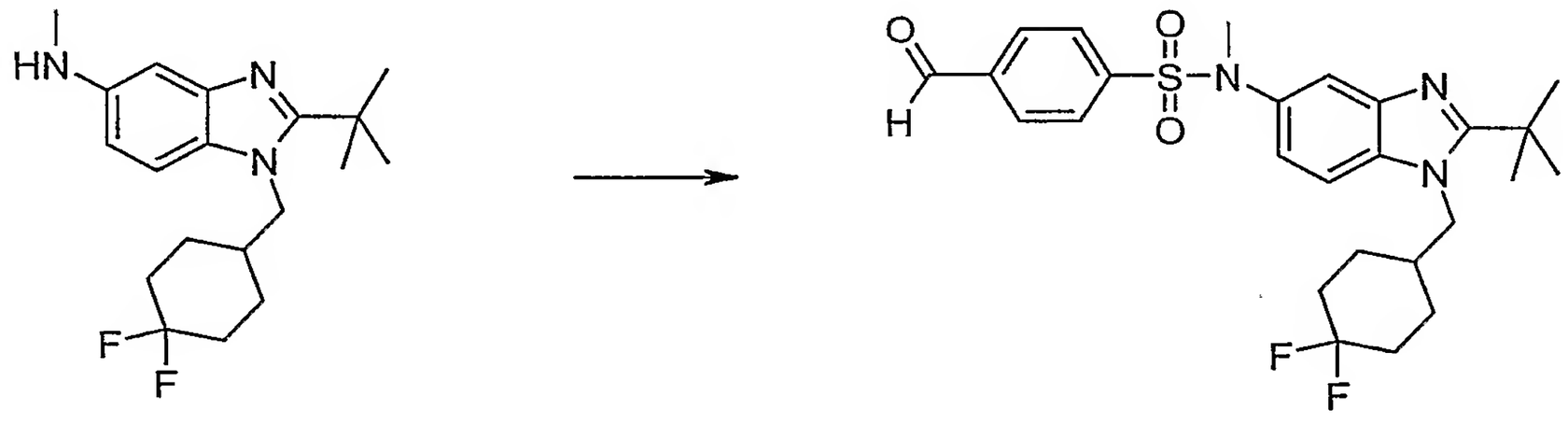
was evaporated and then dissolved in EtOAc (200 mL), washed with saturated sodium bicarbonate solution, brine and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by MPLC using MeOH 5% and acetone 10% in DCM as eluent on silica gel to give 570 mg (65%) of the title compound as a white solid. MS (ESI) $(M+H)^+$: 378.23.

Step G. 2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine



N-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-*N*-methylacetamide (570 mg, 1.51 mmol) and conc. hydrochloric acid (15 mL) were heated together at 80°C for 18 hrs. Upon cooling to room temperature, the reaction mixture was poured into ice-water (100 mL), the pH was brought to13 by using conc. NaOH and the aqueous solution was extracted with EtOAc (3x50 mL). The combined organic layers were washed with brine and dried with Na_2SO_4. After filtration and evaporation, 459 mg (90%) of the title compound was obtained as a white solid. MS (ESI) $(M+H)^+$: 336.04.

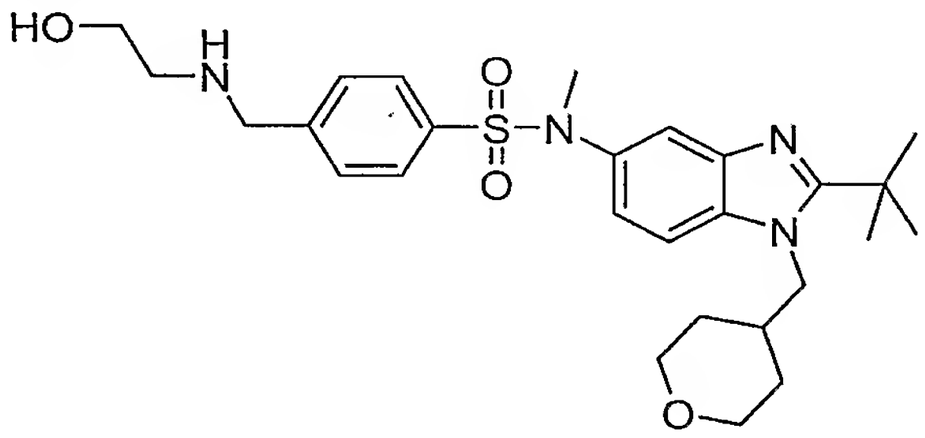
Step H. *N*-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4-formyl-*N*-methylbenzenesulfonamide



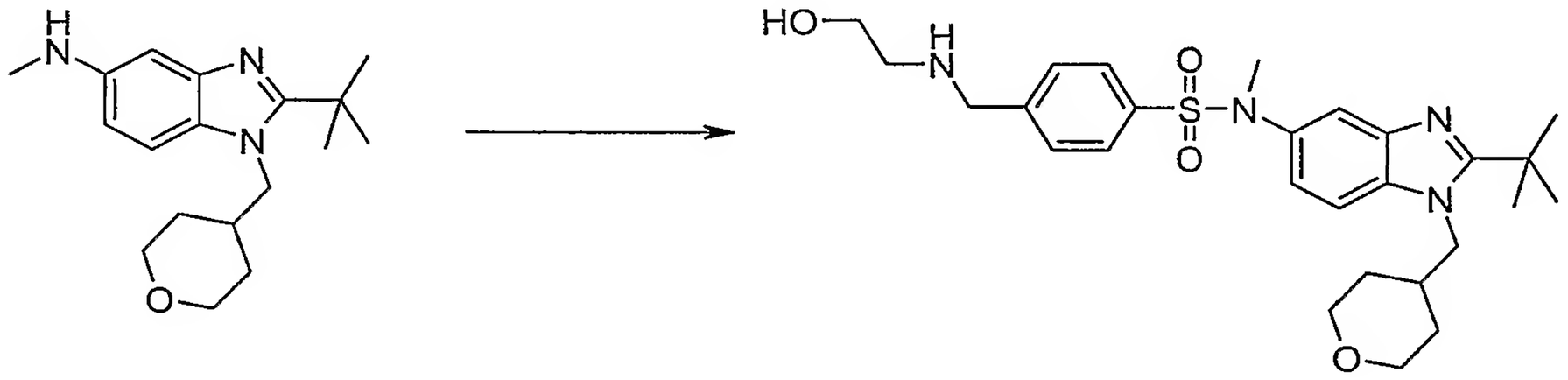
4-formylbenzenesulfonyl chloride (591 mg, 2.89 mmol) was added to a solution of 2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-*N*-methyl-1*H*-benzimidazol-5-amine (808 mg, 2.40 mmol) and DMAP (30 mg, 0.25 mmol) in DCE (15 mL) at room temperature. The reaction mixture was stirred overnight. The solvent was removed; the crude product recovered in EtOAc (250 mL), washed with saturated $NaHCO_3$ solution (3x50 mL), brine and dried over anhydrous Na_2SO_4. The title compound was obtained as a white solid and used for the next step without further purification.

Example 2

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide



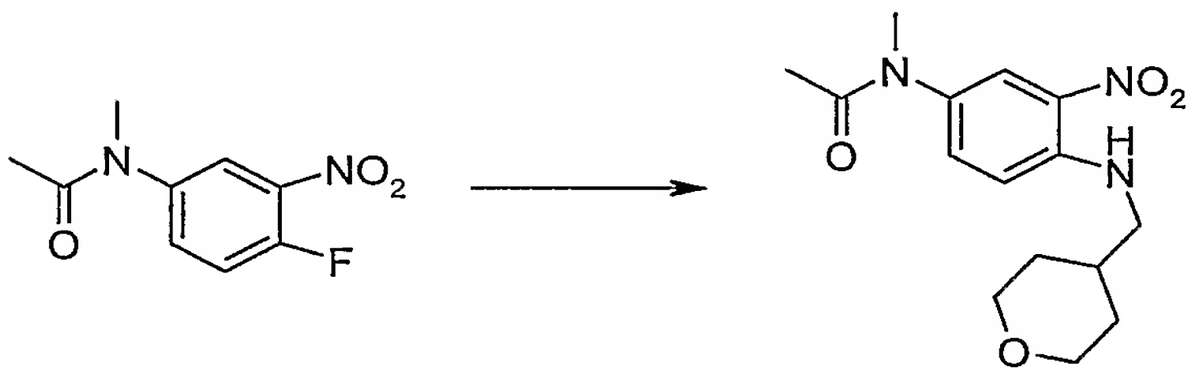
Step A. N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide



2-*tert*-Butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (58 mg, 0.192 mmol) (for preparation, see the following steps B to E) and a catalytic amount of DMAP were dissolved in 5 mL of DCM. 4-Formylbenzenesulfonyl chloride (47 mg, 0.230 mmol) was added and the solution was stirred at rt for 3h. The solution was washed with saturated aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated. The residue was then dissolved in 5 mL of

MeOH containing a few drops of glacial AcOH. Ethanolamine (0.057 mL, 0.960 mmol) and powdered 3Å molecular sieves (500 mg) were added. The solution was stirred at rt for 30 min. $NaCNBH_3$ (36 mg, 0.576 mmol) was added and the solution was stirred at rt for 3h. The solution was filtered and the solvent evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated and the product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 48 mg (40%). ^1H NMR (400 MHz, METHANOL-D_4): δ 1.49 - 1.55 (m, 2 H), 1.55 - 1.61 (m, 2 H), 1.67 (s, 9 H), 2.32 - 2.39 (m, 1 H), 3.15 - 3.18 (m, 2 H), 3.27 (s, 3 H), 3.34 (m, 2 H), 3.81 (dd, *J*=5.96, 4.39 Hz, 2 H), 3.92 (d, *J*=3.12 Hz, 1 H), 3.95 (d, *J*=3.71 Hz, 1 H), 4.33 (s, 2 H), 4.51 (d, *J*=7.62 Hz, 2 H), 7.28 (dd, *J*=9.08, 2.05 Hz, 1 H), 7.56 (d, *J*=1.95 Hz, 1 H), 7.61 - 7.68 (m, 4 H), 7.85 (d, *J*=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 515.0; Anal. Calcd for $C_{27}H_{38}N_4O_4S$ + 2.7 TFA + 0.9 H_2O: C, 46.40; H, 5.11; N, 6.68. Found: C, 46.41; H, 5.05; N, 6.75.

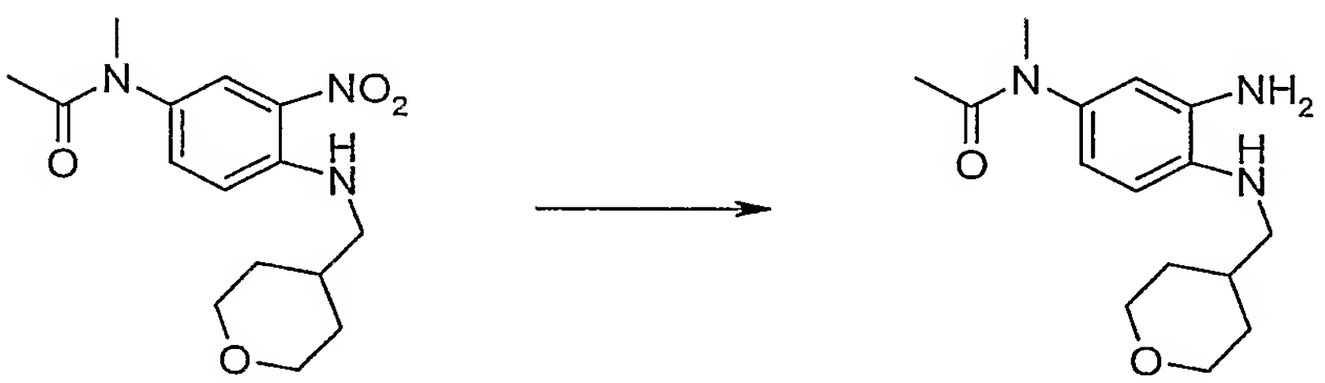
Step B. *N*-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide



4-Aminomethylpyran (2.50 g, 21.7 mmol) was added to a mixture of *N*-(4-fluoro-3-nitrophenyl)-*N*-methylacetamide (4.61 g, 21.27 mmol) (for preparation, see Example 1, Steps B and C) and sodium carbonate (5.10 g, 47.7 mmol) in EtOH (120 mL) at room temperature. The reaction mixture was heated for 3 days at 60 °C. Upon evaporation of ethanol, the residue was dissolved in EtOAc (400 mL), washed with H_2O (3x50 mL), saturated aqueous NaCl solution (3x50 mL), and dried over Na_2SO_4. After filtation and concentration, 6.62 g (100%) of the title compound was obtained as an orange-red solid. ^1H NMR (400 MHz, $CDCl_3$): δ 1.38 - 1.52 (m, 2 H), 1.72 - 1.81 (m, 2 H), 1.90 (s, 3 H), 1.93 - 2.02 (m, 1 H), 3.23 (s, 3 H), 3.23 - 3.27 (m, 2 H), 3.36 -

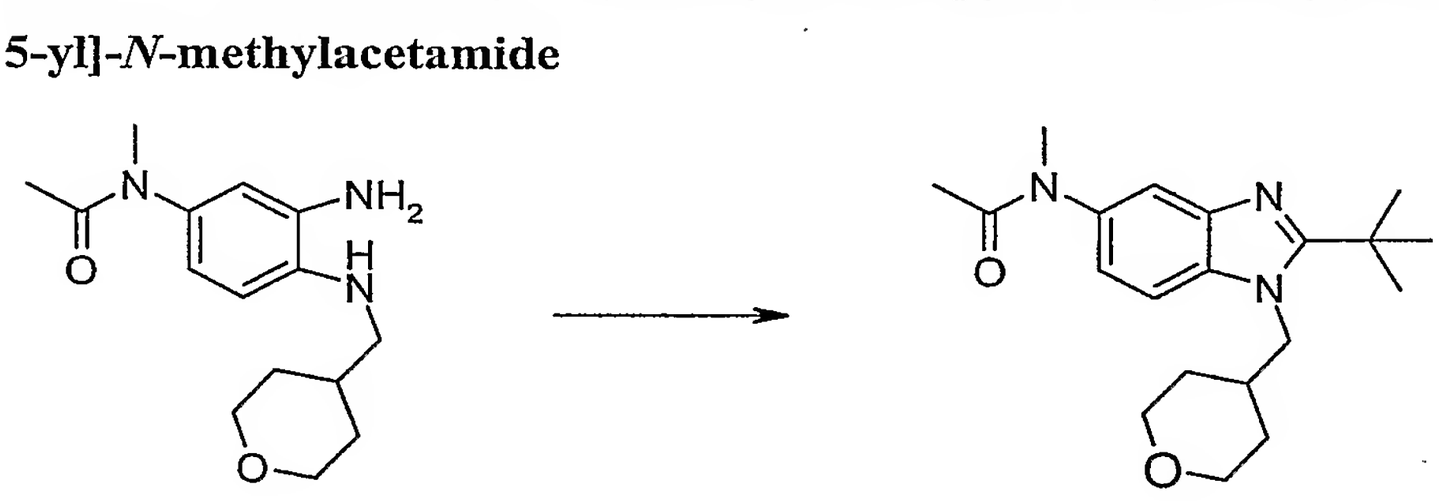
3.49 (m, 2 H), 4.01 - 4.07 (m, 2 H), 6.91 (d, *J*=9.18 Hz, 1 H), 7.29 (dd, *J*=9.08, 2.64 Hz, 1 H), 8.05 (d, *J*=2.34 Hz, 1 H), 8.22 (t, *J*=5.37 Hz, 1 H). MS (ESI) $(M+H)^+$ = 309.12.

Step C. *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide



N-methyl-*N*-{3-nitro-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}acetamide (5.39 g, 16.7 mmol) was hydrogenated in ethyl acetate (200 mL) catalyzed by 10% Pd/C (0.2 g) at 30-40 psi H_2 in Parr shaker for 18 h at room temperature. After filtration through celite and concentration, 6.0 g (100%) of a purple solid was obtained as HCl salt, which was used in the next step without purification. ^{1}H NMR (400 MHz, CD_3OD): δ 1.32 - 1.46 (m, 2 H), 1.78 - 1.84 (m, 2 H), 1.85 (s, 3 H), 1.91 - 2.06 (m, 1 H), 3.16 (d, *J*=6.83 Hz, 2 H), 3.20 (s, 3 H), 3.39 - 3.51 (m, 2 H), 3.94 - 4.03 (m, 2 H), 7.01 (d, *J*=8.59 Hz, 1 H), 7.12 (d, *J*=2.15 Hz, 1 H), 7.17 (dd, *J*=8.49, 4.39 Hz, 1 H). MS (ESI) $(M+H)^+$ = 278.7

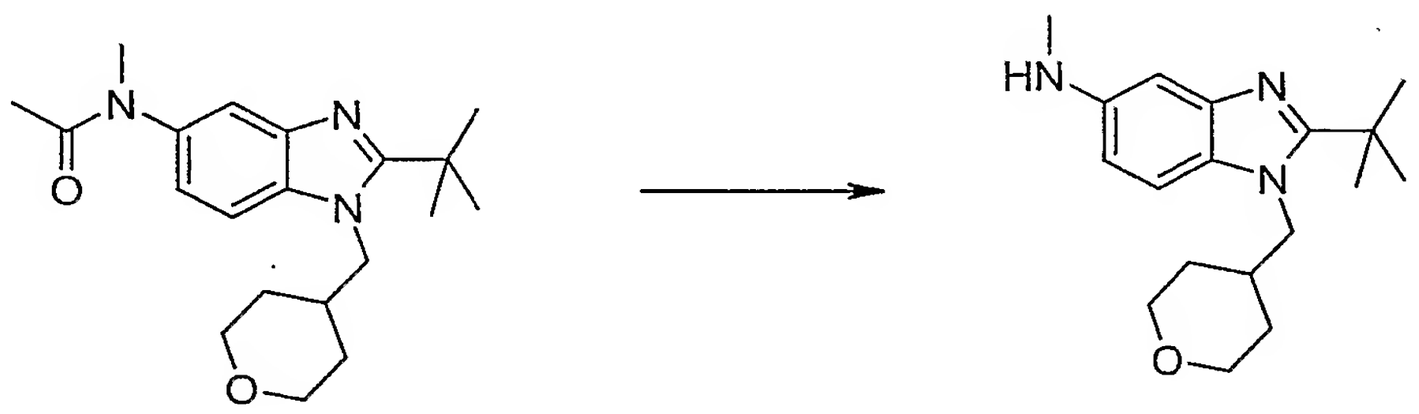
Step D. *N*-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide



Trimethylacetyl chloride (3.27 mL, 3.20 g, 26.5 mmol) was added dropwise to a solution of *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide (7.01 g, 25.3 mmol) and DIPEA (5.3 mL, 3.92 g, 30.36 mmol) in dichloromethane (170 mL) at 0 °C. The resulting mixture was stirred for 4h at room

temperature. After evaporation of the solvent, the residue was dissolved in acetic acid (75 mL) and then divided to 15 sealed test tubes. The mixture was heated at 150°C in a Personal Chemistry SmithSynthesizer microwave instrument for 2.5 h. The combined reaction mixture was evaporated and then dissolved in EtOAc (200 mL), washed with 2 *N* NaOH aqueous solution (2x10 mL), brine (2x10 mL) and dried over Na_2SO_4. After filtration and evaporation, the residue was purified by MPLC using EtOAc/MeOH (10:1) as an eluent on silica gel to give the title compound as a white solid (7.31 g, 84%). MS (ESI) $(M+H)^+$: 344.15.

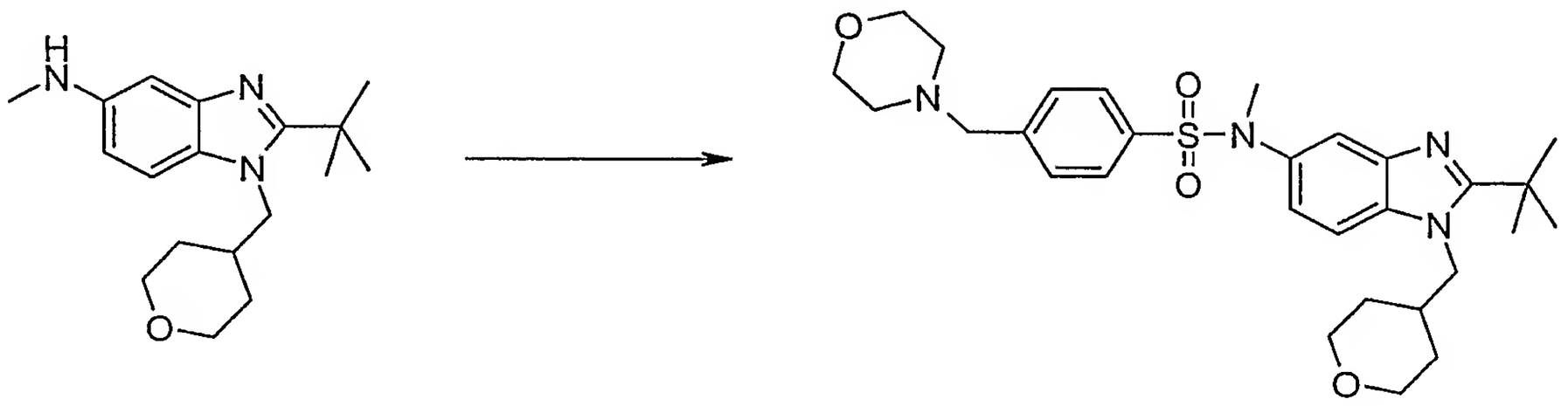
Step E. 2-*tert*-butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



N-[2-*tert*-butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide (4.57g, 13.3 mmol) was dissolved in conc. hydrochloric acid (100 mL) and then heated overnight at 90-100 °C. After concentration, the residue was dissolved in EtOAc (200 mL), washed with 2*N* NaOH (2x20mL) and NaCl (2x20mL), and then dried over Na_2SO_4. After filtration and concentration, 4.02 g (100%) of the title compound was obtained as a purple solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.46 - 1.54 (m, 4 H), 1.54 (s, 9 H), 2.16 - 2.37 (m, 1 H), 2.87 (s, 3 H), 3.23 - 3.38 (m, 2 H), 3.91 - 4.02 (m, 2 H), 4.13 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.15 Hz, 1 H), 6.99 (d, *J*=2.15 Hz, 1 H), 7.11 (d, *J*=8.59 Hz, 1 H). MS (ESI) $(M+H)^+$: 302.06.

Example 3

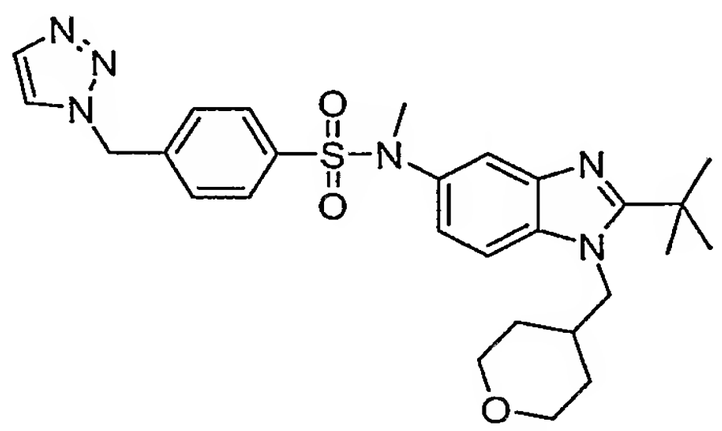
Step A. *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylmethyl)benzenesulfonamide



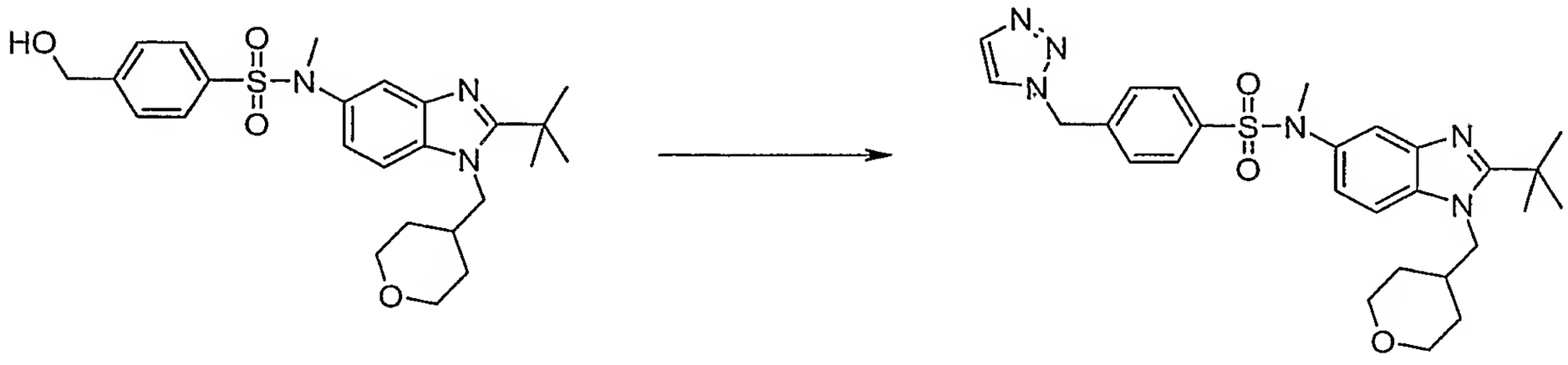
Following the same procedure described in Example 2, Step A, using 2-*tert*-butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (50 mg, 0.166 mmol), DMAP (catalytic) and 4-formylbenzenesulfonyl chloride (44 mg, 0.215 mmol) in 5 mL of DCM. Morpholine (0.045 mL, 0.498 mmol) and $NaCNBH_3$ (31 mg, 0.498 mmol) in 5 mL of MeOH were used for the second step. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and was lyophilized, affording the title compound as the corresponding TFA salt. Yield: 52 mg (48%). ^{1}H NMR (400 MHz, METHANOL-D_4): δ 1.52 - 1.57 (m, 2 H), 1.57 - 1.63 (m, 2 H), 1.68 (s, 9 H), 2.33 - 2.41 (m, 1 H), 3.29 (s, 3 H), 3.29 - 3.32 (m, 4 H), 3.35 (m, 2 H), 3.79 - 3.92 (m, 4 H), 3.93 (d, *J*=3.58 Hz, 1 H), 3.95 (d, *J*=2.82 Hz, 1 H), 4.45 (s, 2 H), 4.53 (d, *J*=7.42 Hz, 2 H), 7.32 (dd, *J*=8.96, 2.05 Hz, 1 H), 7.60 (d, *J*=1.79 Hz, 1 H), 7.65 - 7.72 (m, 4 H), 7.88 (d, *J*=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ 541.0; Anal. Calcd for $C_{29}H_{40}N_4O_4S$ + 2.9 TFA: C, 47.97; H, 4.96; N, 6.43. Found: C, 48.08; H, 5.06; N, 6.13.

Example 4

_N_-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(1*H*-1,2,3-triazol-1-ylmethyl)benzenesulfonamide

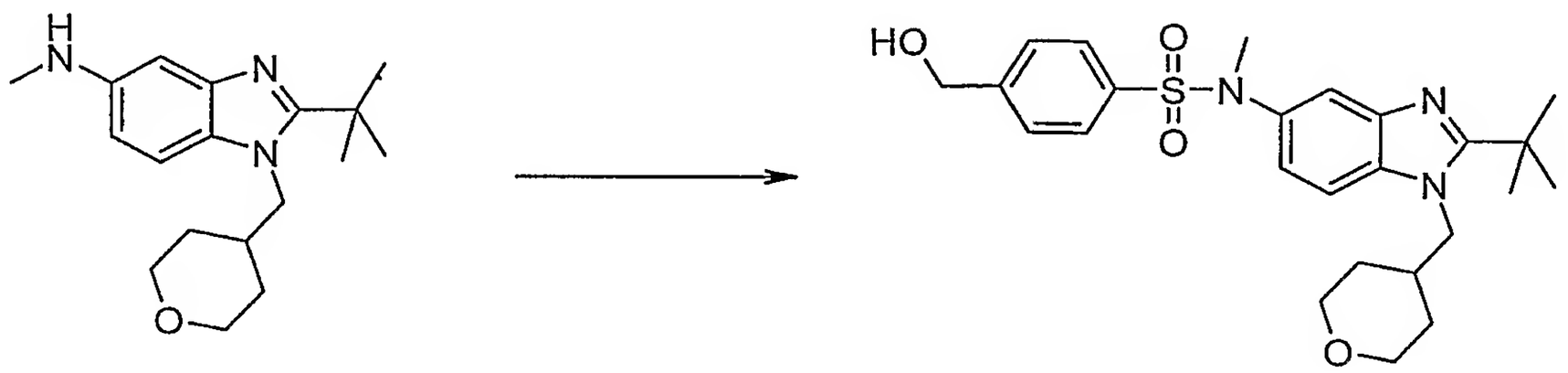


Step A: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(1*H*-1,2,3-triazol-1-ylmethyl)benzenesulfonamide



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(hydroxymethyl)-*N*-methylbenzenesulfonamide (for preparation, see the following Step B) (55 mg, 0.117 mmol) and TEA (0.025 mL, 0.176 mmol) were dissolved in 5 mL of DCM at 0°C. Methanesulfonyl chloride (0.011 mL, 0.140 mmol) was added dropwise and the solution stirred at rt for 3h. The solution was washed with saturated aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated. The residue was then dissolved in 2 mL of DMF and KI (19 mg, 0.117 mmol) followed by addition of 1H-1,2,3-triazole (0.135 mL, 2.34 mmol). The solution was stirred at 80°C for 1h. The solvent was evaporated. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and was lyophilized, affording the title compound as the corresponding TFA salt. Yield: 35 mg (47%). ^1H NMR (400 MHz, METHANOL-D_4): δ 1.50 - 1.56 (m, 2 H), 1.56 - 1.65 (m, 2 H), 1.68 (s, 9 H), 2.32 - 2.40 (m, 1 H), 3.26 (s, 3 H), 3.35 (m, 2 H), 3.93 (d, *J*=3.32 Hz, 1 H), 3.96 (d, *J*=3.51 Hz, 1 H), 4.52 (d, *J*=7.42 Hz, 2 H), 5.74 (s, 2 H), 7.31 (dd, *J*=8.98, 1.95 Hz, 1 H), 7.41 (d, *J*=8.59 Hz, 2 H), 7.54 (s, 1 H), 7.55 - 7.57 (m, 2 H), 7.79 (s, 1 H), 7.88 (d, *J*=8.98 Hz, 1 H), 8.09 (s, 1 H); MS (ESI) $(M+H)^+$ 523.0; Anal. Calcd for $C_{27}H_{34}N_6O_3S$ + 2.4 TFA: C, 47.96; H, 4.61; N, 10.55. Found: C, 48.02; H, 4.72; N, 10.22.

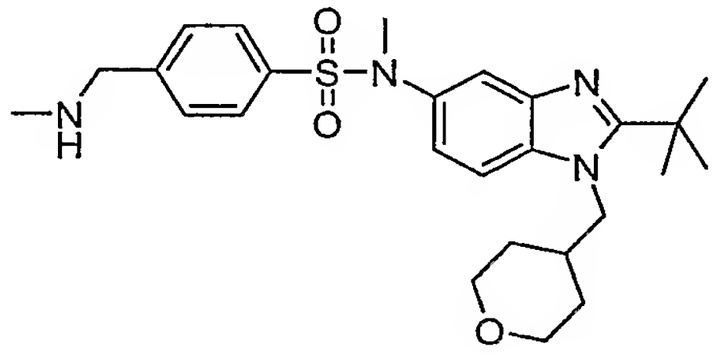
Step B: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(hydroxymethyl)-*N*-methylbenzenesulfonamide



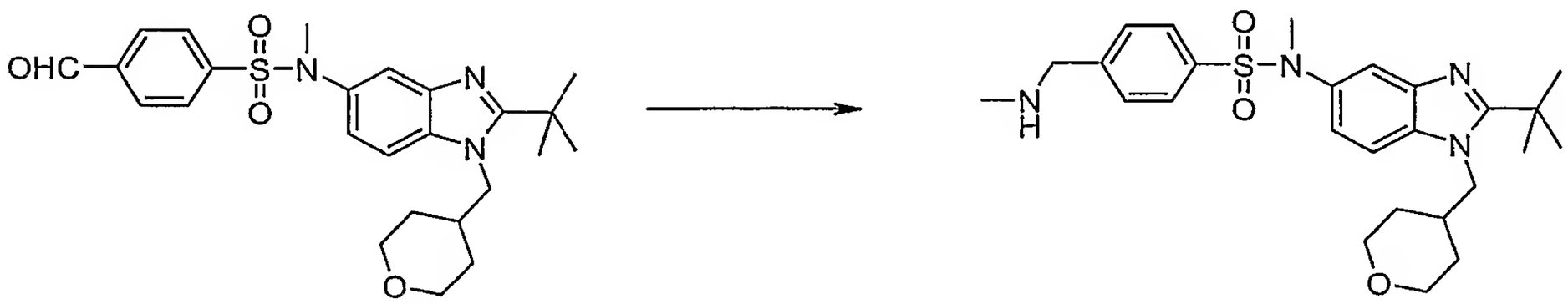
2-*tert*-Butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (45 mg, 0.149 mmol) and a catalytic amount of DMAP were dissolved in 3 mL of DCM. 4-Formylbenzenesulfonyl chloride (37 mg, 0.179 mmol) was added and the solution was stirred at rt for 2h. The solution was washed with saturated aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The solvent was evaporated. The residue was then dissolved in 5 mL of MeOH and $NaCNBH_3$ (20 mg, 0.298 mmol) was added. The solution was stirred overnight at rt. The solvent was evaporated. The residue was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$, brine and dried over anhydrous Na_2SO_4. The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 55 mg (78%). ^{1}H NMR (400 MHz, METHANOL-D_4): δ 1.50 - 1.56 (m, 2 H), 1.57 - 1.65 (m, 2 H), 1.68 (s, 9 H), 2.31 - 2.41 (m, 1 H), 3.26 (s, 3 H), 3.35 (m, 2 H), 3.93 (d, *J*=3.32 Hz, 1 H), 3.96 (d, *J*=3.71 Hz, 1 H), 4.52 (d, *J*=7.42 Hz, 2 H), 4.68 (s, 2 H), 7.30 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.50 (s, 4 H), 7.54 (d, *J*=1.56 Hz, 1 H), 7.87 (d, *J*=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 472.0.

Example 5

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-N-methyl-4-[(methylamino)methyl]benzenesulfonamide

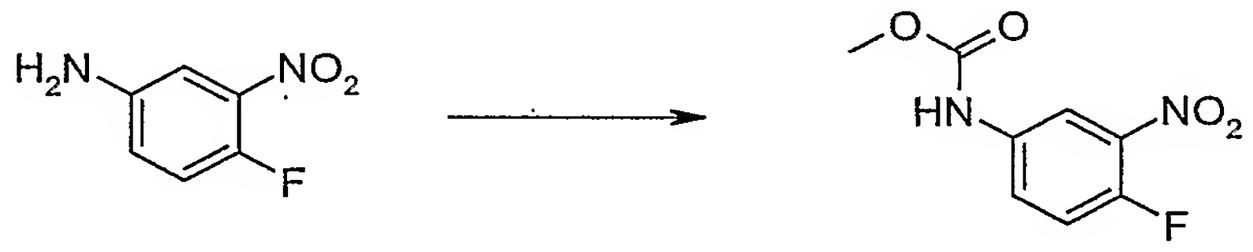


Step A: N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-N-methyl-4-[(methylamino)methyl]benzenesulfonamide



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methylbenzenesulfonamide (for preparation see following steps B to G) (50 mg, 0.106 mmol) was dissolved in 5 mL of MeOH containing a few drops of glacial AcOH and powdered 3Å molecular sieves (400 mg). Methylamine (2M in THF) (0.160 mL, 0.318 mmol) was added and the solution was stirred at rt for 15 min. $Na(CN)BH_3$ (20 mg, 0.318 mmol) was added and the solution was stirred at rt for 3h. The solution was filtered and the solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 14 mg (22%). ^1H NMR (400 MHz, METHANOL-D_4) δ 1.48 - 1.54 (m, 2 H), 1.54 - 1.62 (m, 2 H), 1.65 (s, 9 H), 2.29 - 2.38 (m, 1 H), 2.73 (s, 3 H), 3.26 (s, 3 H,) 3.33 (m, 2 H), 3.91 (d, *J*=3.12 Hz, 1 H), 3.92 - 3.95 (m, 1 H), 4.26 (s, 2 H), 4.49 (d, *J*=7.62 Hz, 2 H), 7.26 (dd, *J*=8.98, 1.95 Hz, 1 H), 7.53 (d, *J*=1.95 Hz, 1 H), 7.63 (d, *J*=1.17 Hz, 4 H), 7.82 (d, *J*=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 485.0.

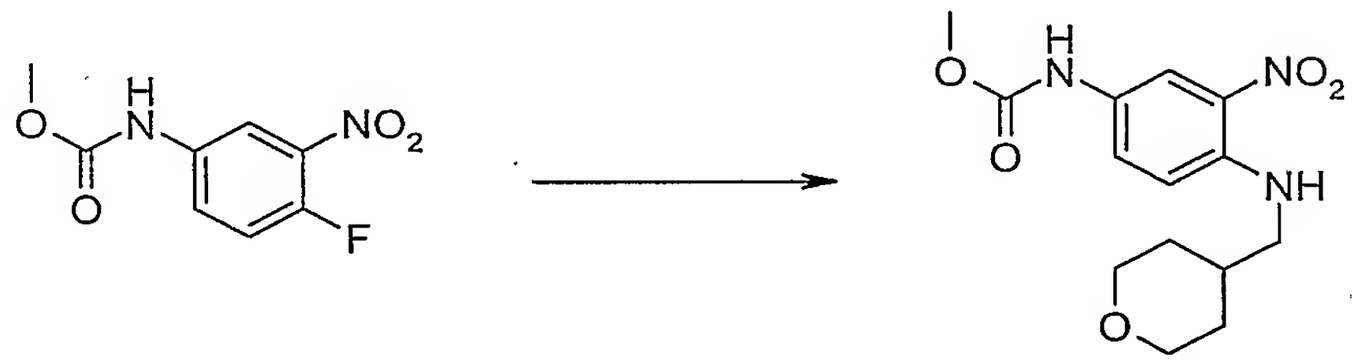
Step B: Methyl (4-fluoro-3-nitrophenyl)carbamate



Methyl chloroformate (13.2 mL, 170.2 mmol) was added dropwise to a cold (0°C) dichloromethane (200 mL) solution of 4-fluoro-3-nitro aniline (24.15 g, 154.7 mmol) and DIPEA (35 mL, 201 mmol). The reaction mixture was stirred at rt overnight. The solution was then diluted with 200 mL of dichloromethane and washed with 2M HCl, brine and dried over anhydrous $MgSO_4$. The solvent was concentrated and the product was directly used for the next step without further purification. Yield: 35.5 g

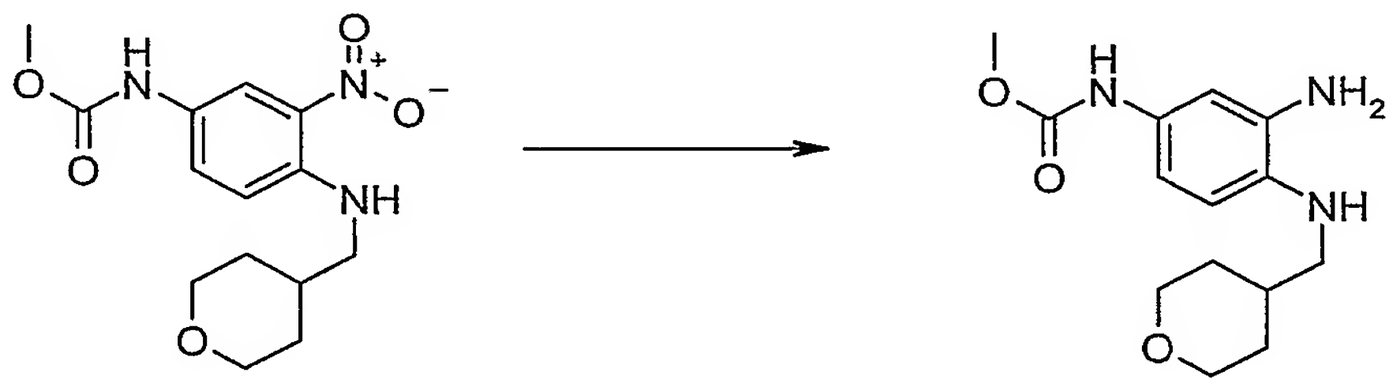
(99%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 3.81 (s, 3H), 7.02 (s, 1H), 7.23 (m, 1H), 7.72 (d, *J* = 8.59Hz, 1H), 8.17 (dd, *J* = 6.35, 2.64Hz, 1H).

Step C: Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate



Methyl (4-fluoro-3-nitrophenyl)carbamate (2.0g, 9.32 mmol) and 4-aminomethyl tetrahydropyran (1.28g, 11.2 mmol) were stirred in 50 mL of EtOH containing TEA (2.0 mL, 14.0 mmol) at 75°C for 48h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous 5% $KHSO_4$, saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 1:1 / hexanes : EtOAc as eluent. Yield: 2.53g (88%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.42 (m, 2 H), 1.73 (d, *J*=1.76 Hz, 1 H), 1.76 (d, *J*=1.95 Hz, 1 H), 1.88 - 2.01 (m, 1 H), 3.22 (m, 2 H), 3.42 (m, 2 H), 3.78 (s, 3 H), 4.01 (d, *J*=4.30 Hz, 1 H), 4.04 (d, *J*=3.51 Hz, 1 H), 6.48 (br.s, 1 H), 6.85 (d, *J*=9.37 Hz, 1 H), 7.65 (br.s, 1 H), 8.03 - 8.09 (m, 2 H).

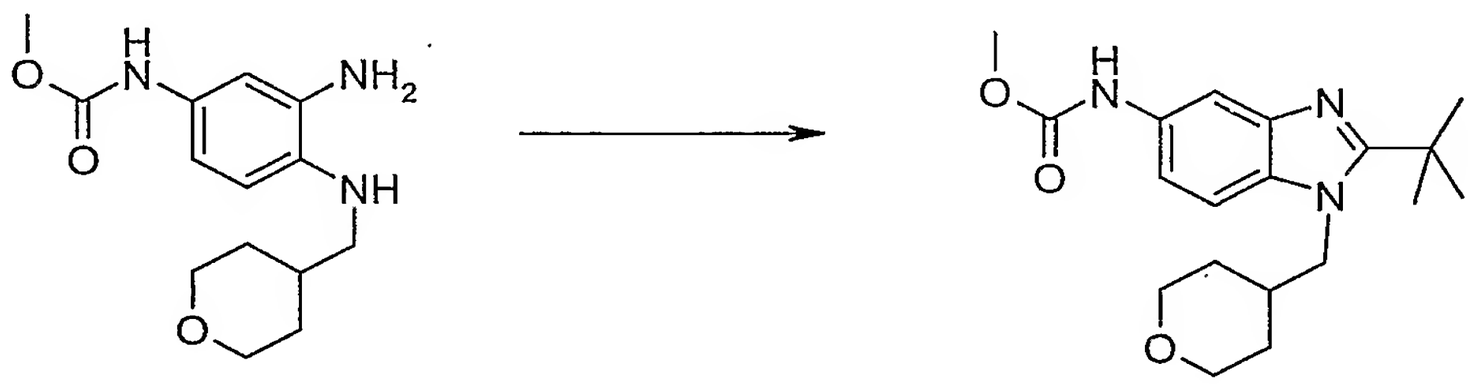
Step D: Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate



Methyl {3-nitro-4-[(tetrahydro-2H-pyran-4-ylmethyl)amino]phenyl}carbamate (2.53g, 8.18 mmol) was dissolved in 50 mL of EtOAc containing a catalytic amount

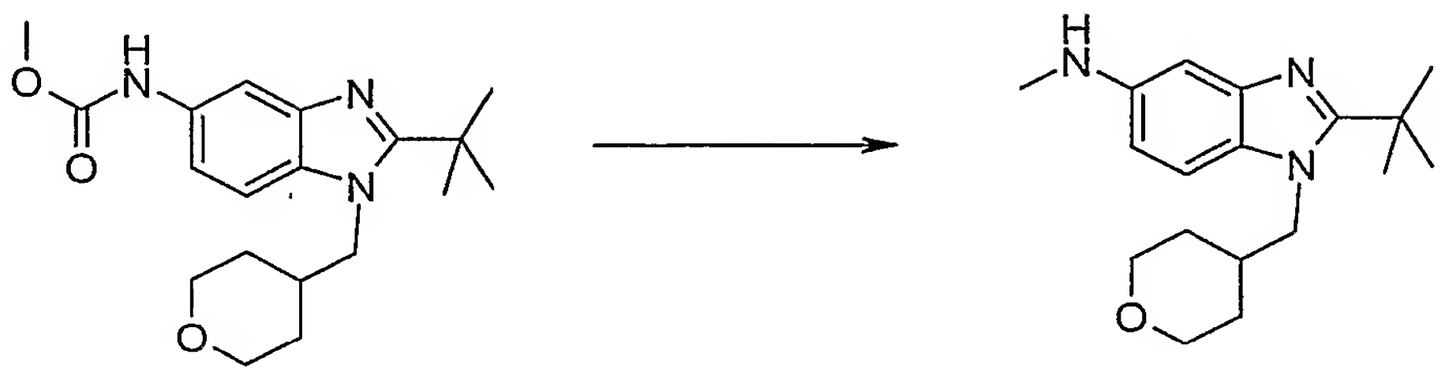
of 10% Pd/C. The solution was shaken under H_2 atmosphere (40 psi) using a Parr hydrogenation apparatus overnight at rt. The solution was filtered through celite and the solvent was evaporated. Yield: 2.29g (99%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.40 (m, 2 H), 1.70 - 1.74 (m, 1 H), 1.74 - 1.77 (m, 1 H), 1.81 - 1.92 (m, 1 H), 2.99 (m, 2 H), 3.34 (br.s, 2 H), 3.41 (m, 2 H), 3.74 (s, 3 H), 3.99 (d, *J*=3.51 Hz, 1 H), 4.02 (d, *J*=3.51 Hz, 1 H), 6.38 (br.s, 1 H), 6.55 - 6.60 (m, 1 H), 6.62 - 6.68 (m, 1 H), 6.95 (br.s, 1 H).

Step E: Methyl [2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate



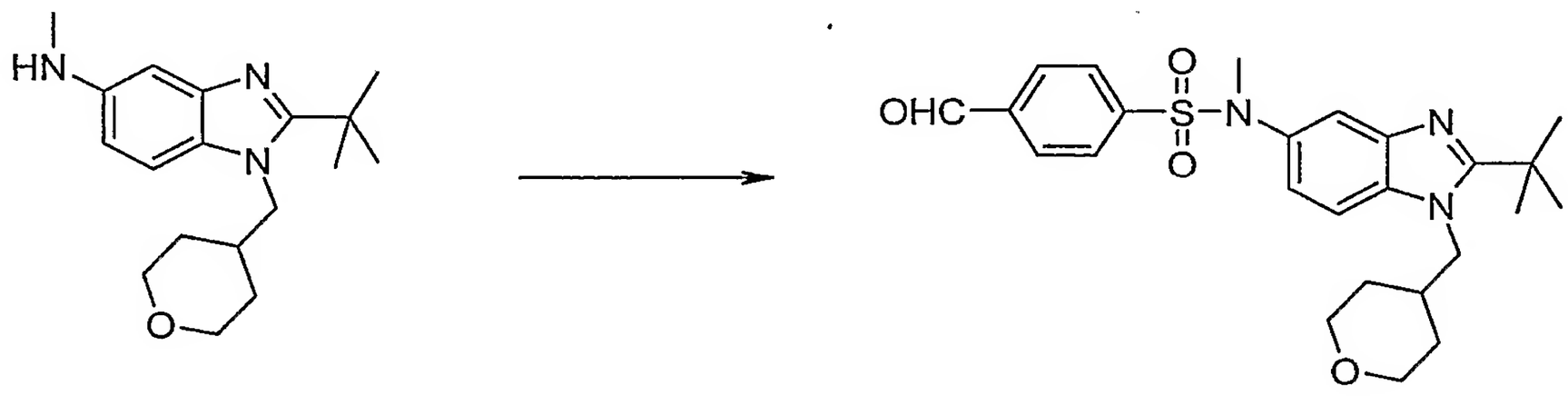
Methyl {3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}carbamate (2.29g, 8.20 mmol) and DMAP (0.20g, 1.64 mmol) were dissolved in 75 mL of DCM. Trimethylacetyl chloride (1.10 mL, 9.02 mmol) was added dropwise and the solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The residue was dissolved in 25 mL of AcOH and was heated at 125°C for 1h using a Personal Chemistry microwave apparatus. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using 4:3 / hexanes : acetone as eluent. Yield: 1.81g (64%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.48 - 1.54 (m, 4 H), 1.56 (s, 9 H), 2.23 - 2.35 (m, 1 H), 3.27 - 3.35 (m, 2 H), 3.78 (s, 3 H), 3.96 (t, *J*=2.93 Hz, 1 H), 3.99 (t, *J*=3.03 Hz, 1 H), 4.18 (d, *J*=7.42 Hz, 2 H), 6.63 (br.s, 1 H), 7.24 - 7.28 (m, 1 H), 7.41 (br.s, 1 H), 7.61 (d, *J*=1.95 Hz, 1 H).

Step F: 2-*tert*-Butyl-N-methyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-amine



Methyl [2-*tert*-butyl-1-(tetrahydro-2H-pyran-4-ylmethyl)-1H-benzimidazol-5-yl]carbamate (1.80g, 5.21 mmol) was dissolved in 75 mL of THF at 0°C. 1M HCl/ether (7.3 mL, 7.29 mmol) was added dropwise and the solution was stirred at 0°C for 15 min. $LiAlH_4$ (988 mg, 26.1 mmol) was added slowly and the solution was stirred at rt overnight. The reaction was quenched at 0°C by the addition of MeOH (5 mL) followed by water (10 mL) and the solution was left to stir at rt for 30 min. Anhydrous Na_2SO_4 (10g) was added and the solution was stirred at rt for another 30 min. The solution was filtered and the solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 1.54g (98%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.49 - 1.53 (m, 4 H), 1.53 - 1.57 (m, 9 H), 2.22 - 2.32 (m, 1 H), 2.87 (s, 3 H), 3.26 - 3.35 (m, 2 H), 3.95 (t, *J*=3.03 Hz, 1 H), 3.97 - 4.00 (m, 1 H), 4.13 (d, *J*=7.42 Hz, 2 H), 6.61 (dd, *J*=8.59, 2.15 Hz, 1 H), 6.99 (d, *J*=1.95 Hz, 1 H), 7.11 (d, *J*=8.59 Hz, 1 H).

Step G: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methylbenzenesulfonamide

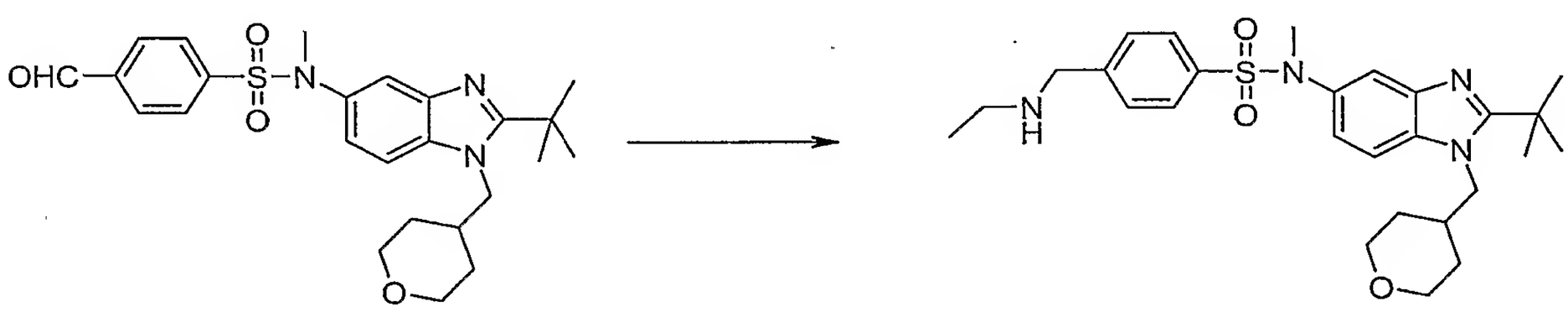


2-*tert*-Butyl-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (250 mg, 0.829 mmol) and DMAP (100 mg, 0.829 mmol) were dissolved in 10 mL of DCM. 4-Formylbenzenesulfonyl chloride (205 mg, 0.995 mmol) was added and the

solution was stirred at rt for 2h. The solution was washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chromatography using EtOAc as eluent. Yield: 288 mg (74%). ^1H NMR (400 MHz, CHLOROFORM-D) δ 1.51 - 1.56 (m, 13 H), 2.25 - 2.34 (m, 1 H), 3.26 (s, 3 H), 3.30 - 3.38 (m, 2 H), 3.99 (t, *J*=2.93 Hz, 1 H), 4.02 (t, *J*=2.93 Hz, 1 H), 4.20 (d, *J*=7.42 Hz, 2 H), 7.19 - 7.21 (m, 1 H), 7.23 (d, *J*=2.15 Hz, 1 H), 7.28 - 7.31 (m, 1 H), 7.76 (d, *J*=8.20 Hz, 2 H), 7.96 (d, *J*=8.59 Hz, 2 H), 10.10 (s, 1 H).

Example 6

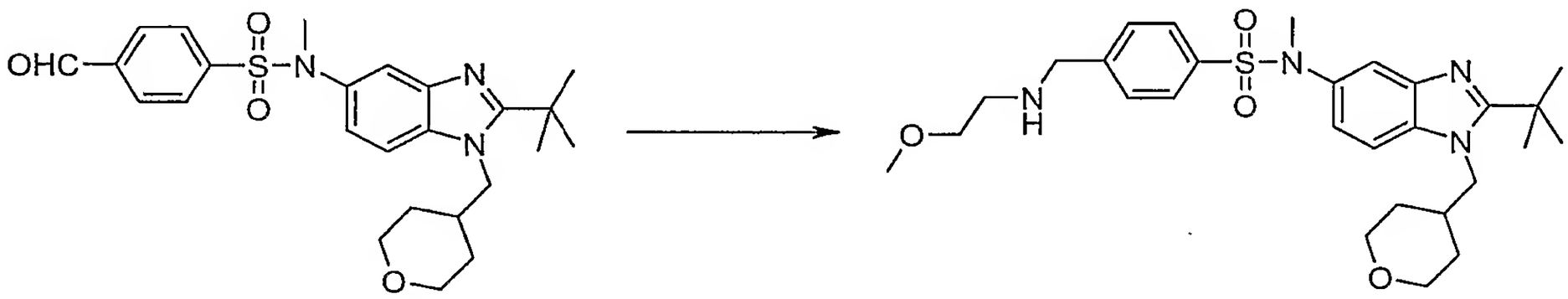
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-[(ethylamino)methyl]-*N*-methylbenzenesulfonamide**



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methylbenzenesulfonamide (50 mg, 0.106 mmol, for preparation, see Example 5 Steps B to G) was dissolved in 5 mL of MeOH containing a few drops of glacial AcOH and powdered 3Å molecular sieves (400 mg). Ethylamine (2M/THF) (0.160 mL, 0.318 mmol) was added and the solution was stirred at rt for 15 min. $Na(CN)BH_3$ (20 mg, 0.318 mmol) was added and the solution was stirred at rt for 3h. The solution was filtered and the solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 20 mg (31%). ^1H NMR (400 MHz, METHANOL-D_4) δ 1.32 (t, *J*=7.32 Hz, 3 H), 1.49 - 1.54 (m, 2 H), 1.54 - 1.63 (m, 2 H), 1.65 (s, 9 H), 2.30 - 2.38 (m, 1 H), 3.13 (m, 2 H), 3.25 (s, 3 H), 3.33 (m, 2 H), 3.91 (d, *J*=2.93 Hz, 1 H), 3.92 - 3.95 (m, 1 H), 4.26 (s, 2 H), 4.49 (d, *J*=7.42 Hz, 2 H), 7.27 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.52 (d, *J*=2.15 Hz, 1 H), 7.63 (s, 4 H), 7.83 (d, *J*=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 499.0.

Example 7

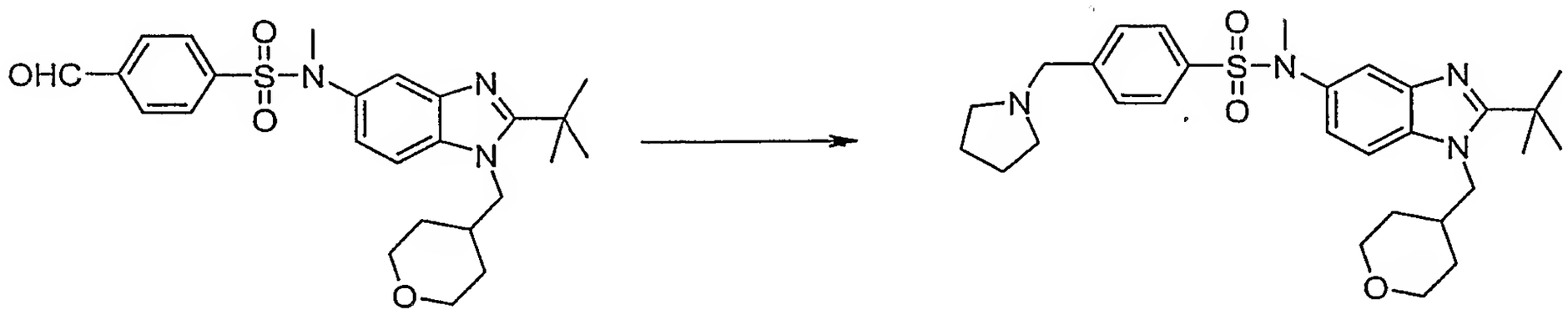
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-{[(2-methoxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide**



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methylbenzenesulfonamide (75 mg, 0.160 mmol, for preparation, see Example 5 Steps B to G) was dissolved in 5 mL of MeOH containing a few drops of glacial AcOH and powdered 3Å molecular sieves (400 mg). 2-Methoxyethylamine (0.070 mL, 0.800 mmol) was added and the solution was stirred at rt for 15 min. $Na(CN)BH_3$ (50 mg, 0.800 mmol) was added and the solution was stirred at rt for 3h. The solution was filtered and the solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 87 mg (85%). ^1H NMR (400 MHz, METHANOL-D_4) δ 1.49 - 1.54 (m, 2 H), 1.55 - 1.63 (m, 2 H), 1.66 (s, 9 H), 2.31 - 2.38 (m, 1 H), 3.23 - 3.26 (m, 2 H), 3.26 (s, 3 H), 3.33 m, 2 H), 3.39 (s, 3 H), 3.63 - 3.66 (m, 2 H), 3.91 (d, *J*=2.93 Hz, 1 H), 3.93 - 3.95 (m, 1 H), 4.31 (s, 2 H), 4.50 (d, *J*=7.42 Hz, 2 H), 7.27 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.57 (d, *J*=1.95 Hz, 1 H), 7.64 (s, 4 H), 7.84 (d, *J*=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 529.0; Anal. Calcd(%) for $C_{28}H_{40}N_4O_4S$ + 3.2 TFA + 0.1 H_2O: C, 46.15; H, 4.89; N, 6.26. Found: C, 46.11; H, 4.66; N, 6.20.

Example 8

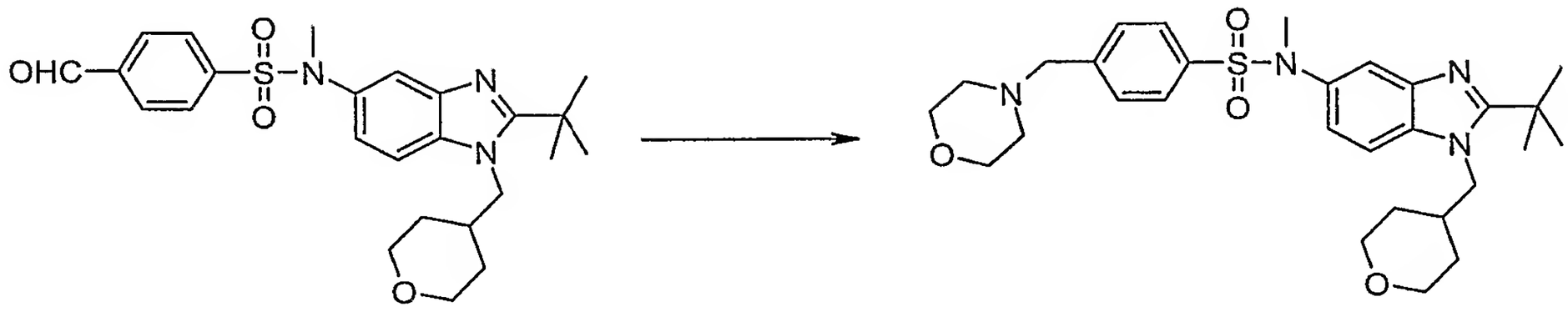
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(pyrrolidin-1-ylmethyl)benzenesulfonamide**



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methylbenzenesulfonamide (75 mg, 0.160 mmol, for preparation, see Example 5 Steps B to G) was dissolved in 5 mL of MeOH containing a few drops of glacial AcOH and powdered 3Å molecular sieves (400 mg). Pyrrolidine (0.068 mL, 0.800 mmol) was added and the solution was stirred at rt for 15 min. $Na(CN)BH_3$ (50 mg, 0.800 mmol) was added and the solution was stirred at rt for 3h. The solution was filtered and the solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 73 mg (71%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.49 - 1.54 (m, 2 H), 1.55 - 1.63 (m, 2 H), 1.66 (s, 9 H), 2.09 (br.s, 4 H), 2.29 - 2.40 (m, 1 H), 3.11 - 3.25 (m, 2 H), 3.27 (s, 3 H), 3.33 (m, 2 H), 3.40 - 3.57 (m, 2 H), 3.91 (d, *J*=2.93 Hz, 1 H), 3.93 - 3.96 (m, 1 H), 4.46 (s, 2 H), 4.51 (d, *J*=7.42 Hz, 2 H), 7.28 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.59 (d, *J*=1.95 Hz, 1 H), 7.66 (d, *J*=1.37 Hz, 4 H), 7.86 (d, *J*=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 525.0; Anal. Calcd(%) for $C_{29}H_{40}N_4O_3S$ + 3.9 TFA + 0.1 H_2O: C, 45.51; H, 4.58; N, 5.77. Found: C, 45.47; H, 4.55; N, 5.95.

Example 9

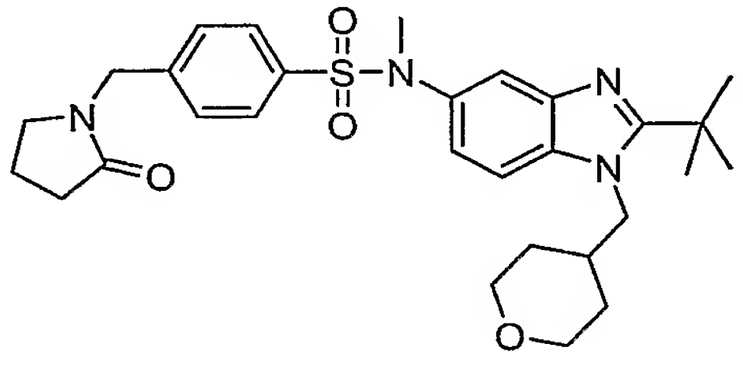
***N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylmethyl)benzenesulfonamide**



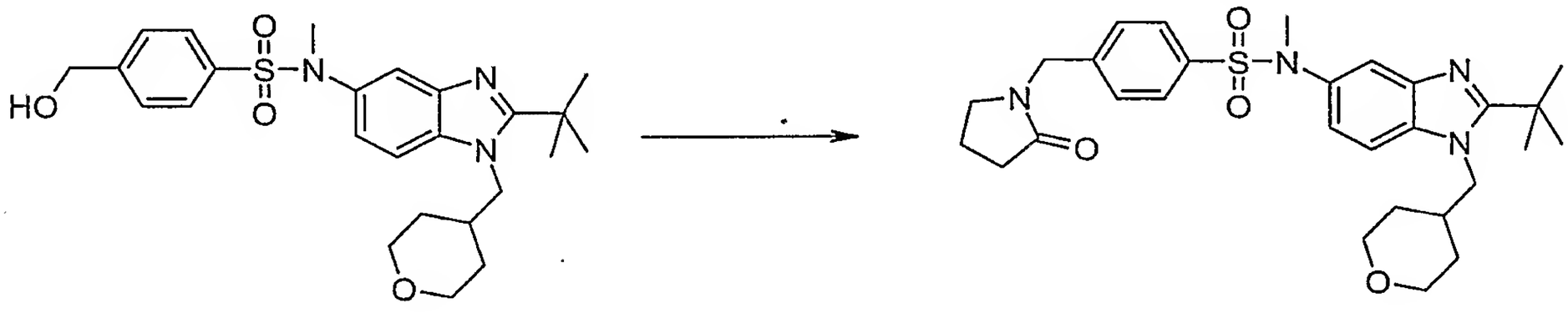
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methylbenzenesulfonamide (77 mg, 0.166 mmol, for preparation, see Example 5 Steps B to G) was dissolved in 5 mL of MeOH containing a few drops of glacial AcOH and powdered 3Å molecular sieves (400 mg). Morpholine (0.045 mL, 0.498 mmol) was added and the solution was stirred at rt for 15 min. $Na(CN)BH_3$ (31 mg, 0.498 mmol) was added and the solution was stirred at rt for 3h. The solution was filtered and the solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 52 mg (48%). ^1H NMR (600 MHz, D_3-MeOD) δ 1.52 - 1.57 (m, 2 H), 1.57 - 1.63 (m, 2 H), 1.68 (s, 9 H), 2.33 - 2.41 (m, 1 H), 3.29 (s, 3 H), 3.29 - 3.32 (m, 4 H), 3.35 (m, 2 H), 3.79 - 3.92 (m, 4 H), 3.93 (d, *J*=3.58 Hz, 1 H), 3.95 (d, *J*=2.82 Hz, 1 H), 4.45 (s, 2 H), 4.53 (d, *J*=7.42 Hz, 2 H), 7.32 (dd, *J*=8.96, 2.05 Hz, 1 H), 7.60 (d, *J*=1.79 Hz, 1 H), 7.65 - 7.72 (m, 4 H), 7.88 (d, *J*=8.96 Hz, 1 H); MS (ESI) $(M+H)^+$ 541.0; Anal. Calcd(%) for $C_{29}H_{40}N_4O_4S$ + 2.9 TFA: C, 47.97; H, 4.96; N, 6.43. Found: C, 48.08; H, 5.06; N, 6.13.

Example 10

_N_-[2-_tert_-Butyl-1-(tetrahydro-2_H_-pyran-4-ylmethyl)-1_H_-benzimidazol-5-yl]-_N_-methyl-4-[(2-oxopyrrolidin-1-yl)methyl]benzenesulfonamide

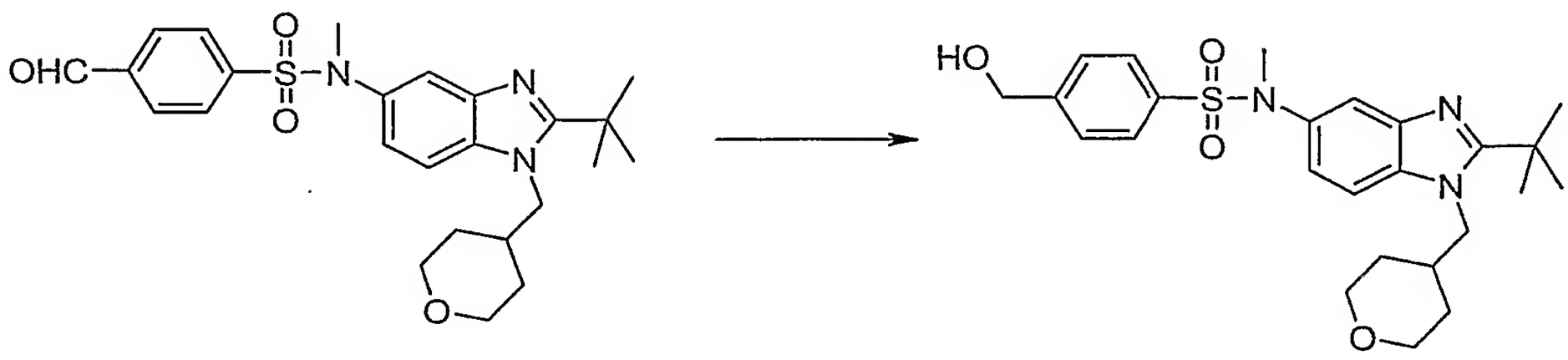


Step A: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-[(2-oxopyrrolidin-1-yl)methyl]benzenesulfonamide



N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(hydroxymethyl)-*N*-methylbenzenesulfonamide (for preparation see following Step B) (60 mg, 0.127 mmol) and TEA (0.021 mL, 0.152 mmol) were dissolved in 5 mL of DCM. Methanesulfonyl chloride (0.011 mL, 0.140 mmol) was added and the solution was stirred at rt for 1h. The solution was washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. The residue was dissolved in 2 mL of DMF and was added dropwise to a stirring solution of 2-pyrrolidinone (32 mg, 0.381 mmol) and NaH (15 mg, 0.381 mmol) in 3 mL of DMF at 0°C. The solution was then stirred at rt for 2h. The reaction was quenched with the addition of saturated aqueous $NaHCO_3$ and the solvent was evaporated. The product was dissolved in EtOAc and washed with saturated aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The product was purified by reversed-phase HPLC using 10-70% CH_3CN/H_2O and lyophilized affording the title compound as the corresponding TFA salt. Yield: 31 mg (37%). ^{1}H NMR (400 MHz, METHANOL-D_4) δ 1.49 - 1.54 (m, 2 H), 1.55 - 1.63 (m, 2 H), 1.66 (s, 9 H), 2.00 - 2.09 (m, 2 H), 2.31 - 2.38 (m, 1 H), 2.43 (m, 2 H), 3.24 (s, 3 H), 3.30 - 3.38 (m, 4 H), 3.91 (d, *J*=3.12 Hz, 1 H), 3.92 - 3.95 (m, 1 H), 4.48 - 4.52 (m, 4 H), 7.29 (dd, *J*=8.98, 2.15 Hz, 1 H), 7.38 (d, *J*=8.59 Hz, 2 H), 7.51 (d, *J*=8.40 Hz, 2 H), 7.53 (d, *J*=1.95 Hz, 1 H), 7.86 (d, *J*=8.98 Hz, 1 H); MS (ESI) $(M+H)^+$ 538.8; Anal. Calcd(%) for $C_{29}H_{38}N_4O_4S$ + 1.8 TFA: C, 52.63; H, 5.39; N, 7.53. Found: C, 52.78; H, 5.00; N, 7.92.

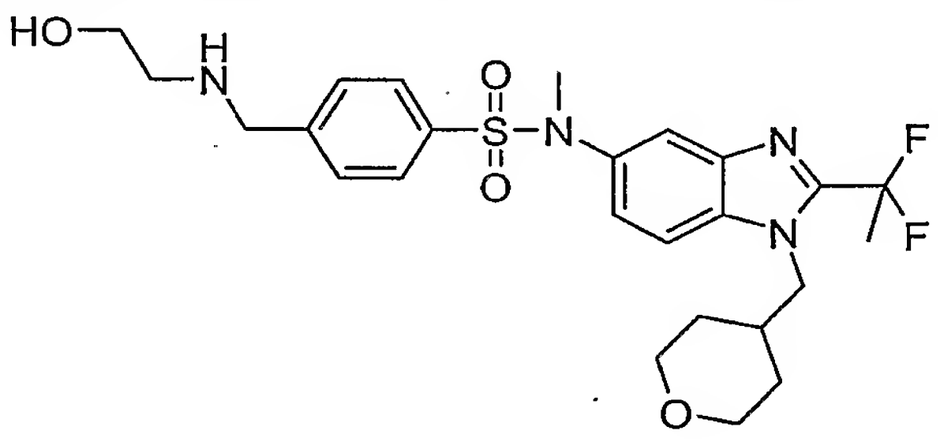
Step B: *N*-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-(hydroxymethyl)-*N*-methylbenzenesulfonamide



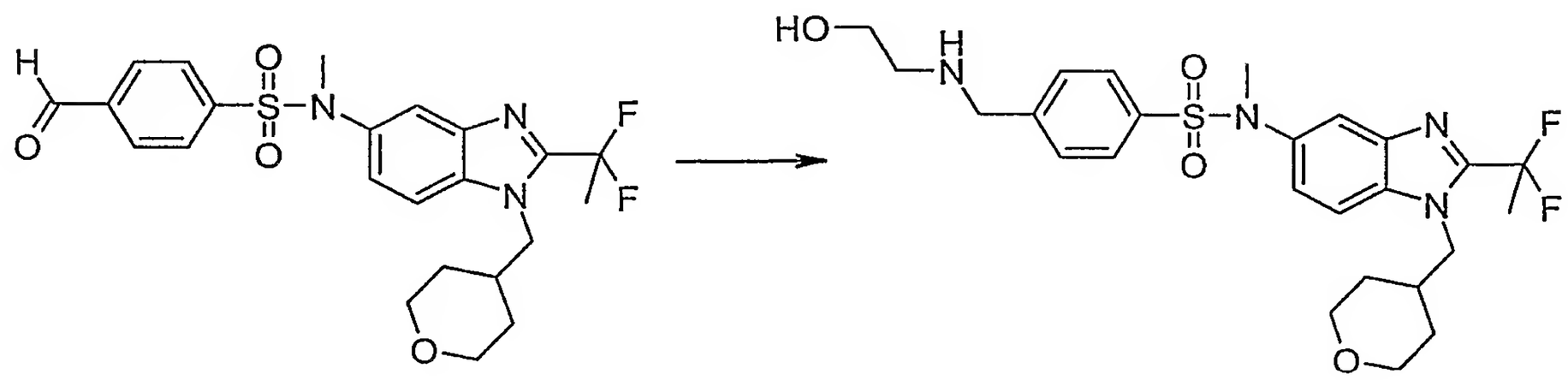
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methylbenzenesulfonamide (115 mg, 0.245 mmol, for preparation, see Example 5 Steps B to G) was dissolved in 8 mL of 1:1 / THF:MeOH at 0°C. $NaBH_4$ (19 mg, 0.490 mmol) was added and the solution was stirred at rt for 1h. The solvent was evaporated. The residue was dissolved in EtOAc and washed with aqueous $NaHCO_3$ solution, brine and dried over anhydrous $MgSO_4$. The solvent was evaporated. Yield: 116 mg (99%). ^{1}H NMR (400 MHz, CHLOROFORM-D) δ 1.50 - 1.57 (m, 13 H), 2.21 (s, 1 H), 2.25 - 2.35 (m, 1 H), 3.21 (s, 3 H), 3.30 - 3.38 (m, 2 H), 3.98 (m, 1 H), 4.01 (m, 1 H), 4.19 (d, *J*=7.42 Hz, 2 H), 4.78 (s, 2 H), 7.16 - 7.18 (m, 1 H), 7.27 - 7.29 (m, 2 H), 7.44 (d, *J*=8.59 Hz, 2 H), 7.57 (d, *J*=8.59 Hz, 2 H).

Example 11

_N_-[2-(1,1-Difluoroethyl)-1-(tetrahydro-2_H_-pyran-4-ylmethyl)-1_H_-benzimidazol-5-yl]-4-{[(2-hydroxyethyl)amino]methyl}-_N_-methylbenzenesulfonamide

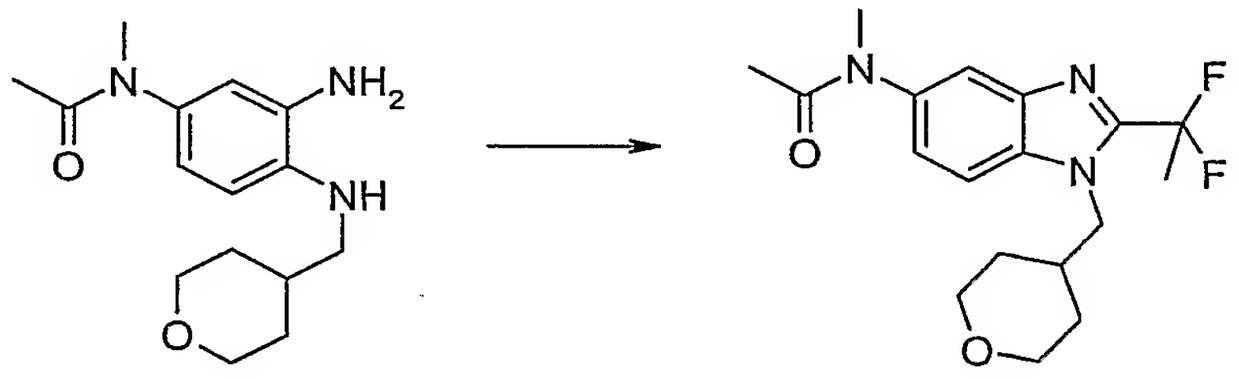


Step A. _N_-[2-(1,1-Difluoroethyl)-1-(tetrahydro-2_H_-pyran-4-ylmethyl)-1_H_-benzimidazol-5-yl]-4-{[(2-hydroxyethyl)amino]methyl}-_N_-methylbenzenesulfonamide



Ethanolamine (0.57 mL, 9.50 mmol) was added to a mixture of *N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methylbenzenesulfonamide (454 mg, 0.95 mmol) (for preparation, see the following steps B to D) and MeOH (15 mL). The reaction mixture was stirred for 30 min. and AcOH (2 drops) was added. The reaction mixture was stirred for 1 hr. and $NaBH_4$ was added. The reaction mixture was stirred for 3hrs. and the solvent was evaporated. The product was purified by reverse-phase preparative HPLC using MeCN 10 to 90% gradient in water to provide the TFA salt of the title compound as white solid. Yield: 420 mg (84%); ^{1}H NMR (400 MHz, CD_3OD) δ 1.38 - 1.54 (m, 4 H), 2.20 m, 3 H), 2.27 - 2.34 (m, 1 H), 3.14 - 3.21 (m, 2 H), 3.27 (s, 3 H), 3.31 - 3.38 (m, 1 H), 3.83 (m, 2 H), 3.87 - 3.96 (m, 2 H), 4.30 - 4.37 (m, 4 H), 7.23 - 7.32 (m, 2 H), 7.59 - 7.70 (m, 5 H); MS (ESI) $(M+H)^+$ 523.0; Anal. Calcd for $C_{25}H_{32}F_2N_4O_4S$ + 2.6 TFA + 0.1 H_2O: C, 44.19; H, 4.27; N, 6.83. Found: C, 44.27; H, 4.25; N, 6.60.

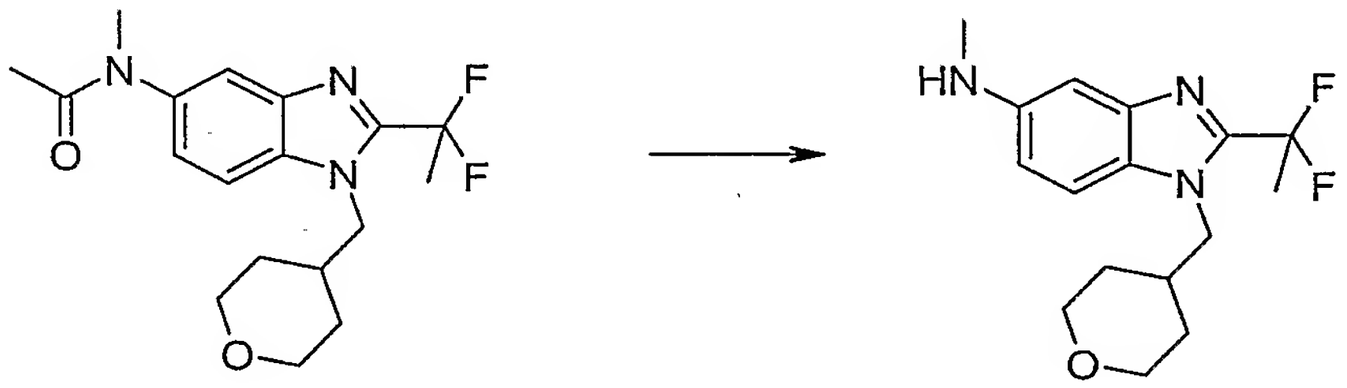
Step B. *N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide



HATU (3.76 g, 9.91 mmol) and *N*-{3-amino-4-[(tetrahydro-2*H*-pyran-4-ylmethyl)amino]phenyl}-*N*-methylacetamide (2.50 g, 9.01 mmol) (for preparation, see Steps B and C in Example 2) were added to a solution of 2,2-difluoropropanoic acid (0.99 g, 9.01 mmol) and DIPEA (1.88 mL, 10.8 mmol) in DMF (100 mL) at 0°C.

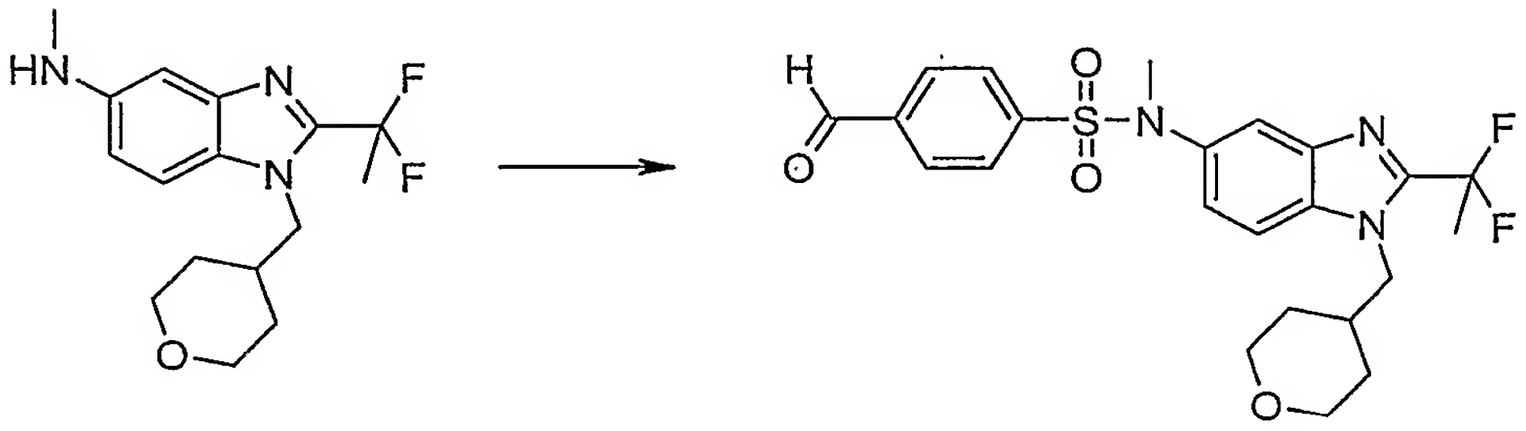
The reaction mixture was stirred for 5 hrs and the solvent was concentrated. The intermediate was heated to 80°C for 2 hrs in glacial AcOH (100 mL), and the solvent was concentrated. The crude product was recovered in DCM (300 mL), washed with saturated $NaHCO_3$ solution (3 x 100 mL), brine and dried over anhydrous $MgSO_4$. The solvent was concentrated and the product was purified by normal-phase MPLC using MeOH 3% and Acetone 5% in DCM to provide the title compound as pale pink solid. Yield: 2.40 g (76%); MS (ESI) $(M+H)^+$ 352.3.

Step C. 2-(1,1-difluoroethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine



A mixture of *N*-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methylacetamide (2.40 g, 6.82 mmol) and concentrated HCl (15 mL) was heated to 80°C overnight. The reaction mixture was cooled to rt, poured into water (100 mL) and the resulting mixture was neutralized to pH 8 using NaOH solution. The product was extracted with EtOAc (4 x 100 mL) and the combined organic layers were washed with saturated $NaHCO_3$ solution and brine. The solution was dried over anhydrous Na_2SO_4 and the solvent was concentrated to provide the title compound as pale green oil. Yield: 1.96 g (92%); MS (ESI) $(M+H)^+$ 310.1.

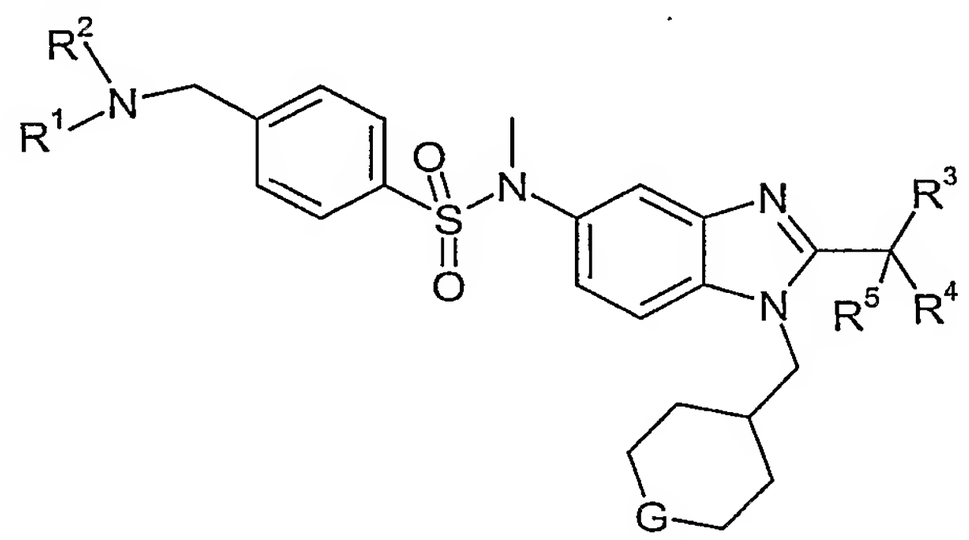
Step D. *N*-[2-(1,1-Difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-formyl-*N*-methylbenzenesulfonamide



4-Formylbenzenesulfonyl chloride (238 mg, 1.16 mmol) was added to a solution of 2-(1,1-difluoroethyl)-*N*-methyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-amine (300 mg, 0.96 mmol), DIPEA (0.23 mL, 1.35 mmol) and DMAP (118 mg, 0.96 mmol). The reaction mixture was heated to 60°C overnight and the solvent was concentrated. The product was recovered in EtOAc and washed with saturated $NaHCO_3$ solution, water and brine. The organic solution was dried over anhydrous Na_2SO_4 and the solvent was concentrated. The product was purified on silica gel by MPLC using EtOAc 10 to 90% in heptane to provide the title compound as white solid. Yield: 454 mg (98%); MS (ESI) $(M+H)^+$ 478.2.

What is claimed is:

1. A compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

G is selected from –O- and $–CF_2$-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, and C_{1-4}alkoxy; or R^1 and R^2 together with the N to which they are bound may form a C_{3-6}heterocycle; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

2. A compound as claimed in claim 1, wherein

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl, and hydroxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl; or R^1 and R^2 together with the N to which they are bound may form a C_{2-5}heterocycloalkyl; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

3. A compound as claimed in claim 1, wherein

G is –O-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl and hydroxy-C_{1-4}alkyl, and C_{1-4}alkoxy-C_{1-4}alkyl with R^1 and R^2 being different groups; or R^1 and R^2 together with the N to which they are bound may form a group selected from 2-oxopyrrolidin-1-yl, pyrrolidin-1-yl, 1*H*-1,2,3-triazol-1-yl, and morpholinyl group; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl with R^3, R^4 and R^5 being the same.

4. A compound as claimed in claim 1, wherein

G is $-CF_2-$;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl and hydroxy-C_{1-4}alkyl, and C_{1-4}alkoxy-C_{1-4}alkyl with R^1 and R^2 being different groups; and

R^3, R^4 and R^5 are each independently methyl.

5. A compound selected from

N-{2-*tert*-butyl-1-[(4,4-difluorocyclohexyl)methyl]-1*H*-benzimidazol-5-yl}-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(morpholin-4-ylmethyl)benzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(1*H*-1,2,3-triazol-1-ylmethyl)benzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-[(methylamino)methyl]benzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-[(ethylamino)methyl]-*N*-methylbenzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-{[(2-methoxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide;

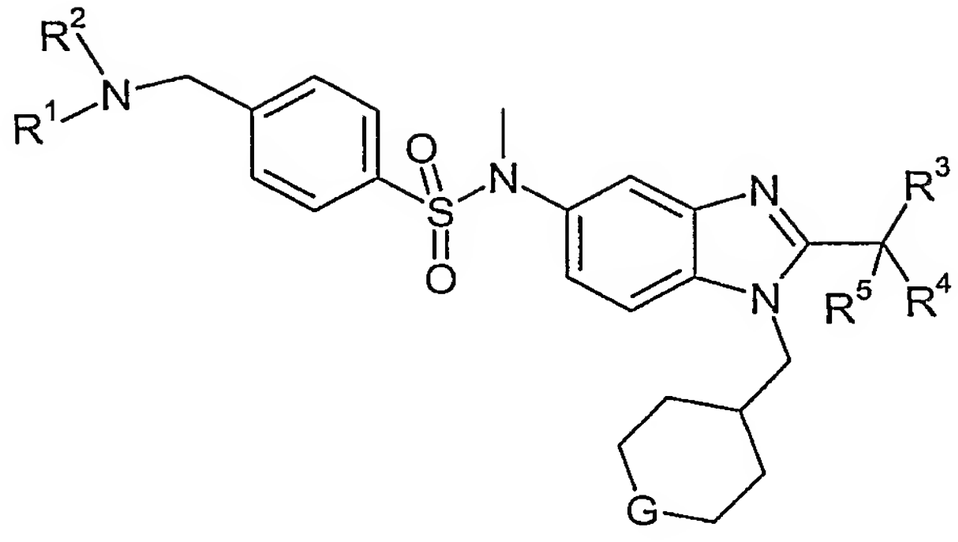
N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-(pyrrolidin-1-ylmethyl)benzenesulfonamide;

N-[2-*tert*-Butyl-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-*N*-methyl-4-[(2-oxopyrrolidin-1-yl)methyl]benzenesulfonamide;

N-[2-(1,1-difluoroethyl)-1-(tetrahydro-2*H*-pyran-4-ylmethyl)-1*H*-benzimidazol-5-yl]-4-{[(2-hydroxyethyl)amino]methyl}-*N*-methylbenzenesulfonamide;

and pharmaceutically acceptable salts thereof.

6. A compound of formula I, a pharmaceutically acceptable salt thereof, diastereomers, enantiomers, or mixtures thereof:



I

wherein

G is selected from –O-, -CHF- and $–CF_2$-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, and C_{1-4}alkoxy; or R^1 and R^2 together with the N to which they are bound may form a C_{3-6}heterocycle; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

7. A compound according to any one of claims 1-6 for use as a medicament.

8. The use of a compound according to any one of claims 1-6 in the manufacture of a medicament for the therapy of pain.

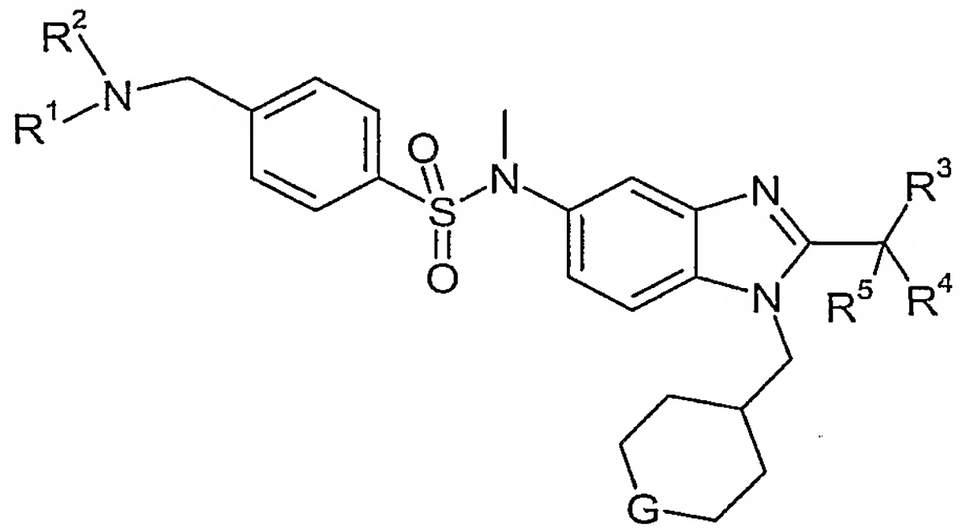
9. The use of a compound according to any one of claims 1-6 in the manufacture of a medicament for the treatment of anxiety disorders.

10. The use of a compound according to any one of claims 1-6 in the manufacture of a medicament for the treatment of cancer, multiple sclerosis, Parkinson's disease, Huntington's chorea, Alzheimer's disease, gastrointestinal disorders and cardiovascular disorders.

11. A pharmaceutical composition comprising a compound according to any one of claims 1-6 and a pharmaceutically acceptable carrier.

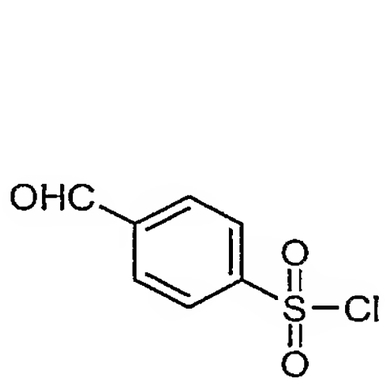
12. A method for the therapy of pain in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of a compound according to any one of claims 1-6.

13. A method for preparing a compound of Formula I, comprising:

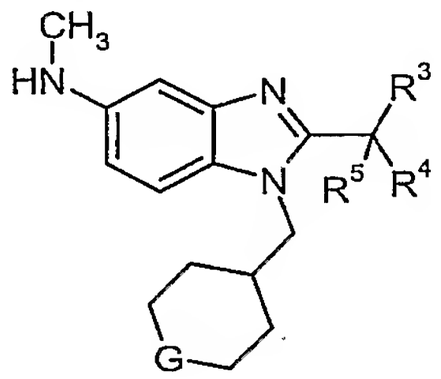


I

reacting a compound of Formula II with a compound of formula III,



II



III

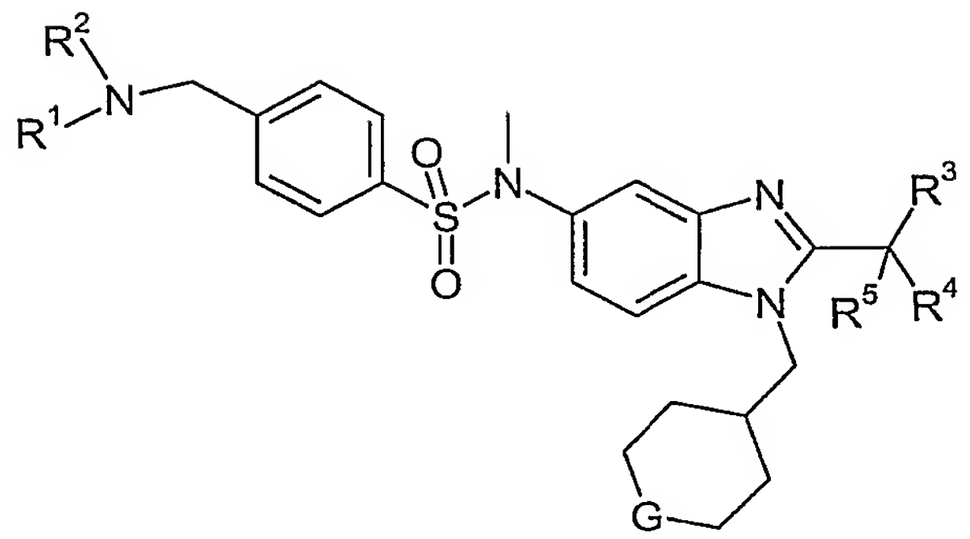
followed by reductive amination with $R^1(R^2)NH$ in the presence of a reducing reagent wherein

G is selected from –O-, -CHF- and $–CF_2$-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, and C_{1-4}alkoxy; or R^1 and R^2 together with the N to which they are bound may form a C_{3-6}heterocycle; and

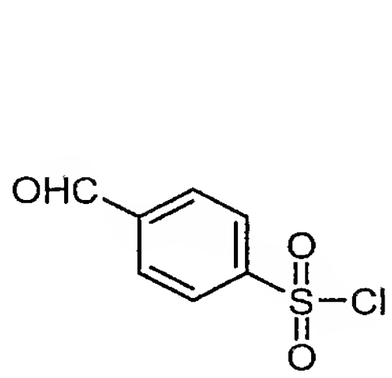
R^3, R^4 and R^5 are independently selected from fluoro and methyl.

14. A method for preparing a compound of Formula I, comprising:

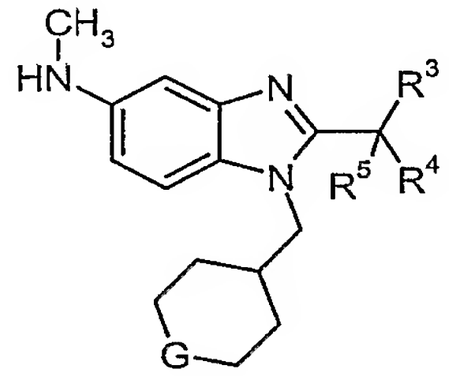


I

reacting a compound of Formula II with a compound of formula III,



II



III

followed by a sequence of reactions including 1) reduction with a reducing agent, 2) methanesulfonylation and 3) nucleophilic substitution with $R^1(R^2)NH$,

wherein

G is selected from –O-, -CHF- and $–CF_2$-;

R^1 and R^2 are independently selected from –H, C_{1-4}alkyl, hydroxy-C_{1-4}alkyl, C_{1-4}alkoxy-C_{1-4}alkyl, and C_{1-4}alkoxy; or R^1 and R^2 together with the N to which they are bound may form a C_{3-6}heterocycle; and

R^3, R^4 and R^5 are independently selected from fluoro and methyl.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 101696-1 WO	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below.
International application No. PCT/SE 2005/001399	International filing date *(day/month/year)* 22 Sept 2005	(Earliest) Priority Date *(day/month/year)* 24 Sept 2004
Applicant AstraZeneca AB et al		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 5 sheets.

☐ It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the language, the international search was carried out on the basis of:

   ☒ the international application in the language in which it was filed

   ☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

   b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☒ **Certain claims were found unsearchable** (see Box No. II)

3. ☐ **Unity of invention is lacking** (see Box No. III)

4. With regard to the **title**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   ☒ the text is approved as submitted by the applicant.

   ☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. With regard to the **drawings**,

   a. the figure of the drawings to be published with the abstract is Figure No. _____

   ☐ as suggested by the applicant.

   ☐ as selected by this Authority, because the applicant failed to suggest a figure.

   ☐ as selected by this Authority, because this figure better characterizes the invention.

   b. ☐ none of the figures is to be published with the abstract.

Continuation of cover sheet

C07D 405/06 (2006.01)
A61K 31/4184 (2006.01)
A61P 25/22 (2006.01)
A61P 29/02 (2006.01)
C07D 235/08 (2006.01)
C07D 235/10 (2006.01)
C07D 405/14 (2006.01)
C07D 413/14 (2006.01).

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2005/001399

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 12 relates to a method of treatment of the human by therapy /Rule 39.1(iv). Nevertheless, a search has been executed for this claim. The search has been based on the alleged effects of the compounds.

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/001399

A. CLASSIFICATION OF SUBJECT MATTER

IPC7: see extra sheet
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-INTERNAL, WPI DATA, PAJ, CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005030761 A1 (ASTRAZENECA AB), 7 April 2005 (07.04.2005), examples 53-54	1-13
P,X	WO 2005030762 A1 (ASTRAZENECA AB), 7 April 2005 (07.04.2005), examples 33-34	1-13
A	US 20040116465 A1 (CHENG ET AL), 17 June 2004 (17.06.2004), paragraphs [0001]-[0003], examples 95-96	1-13
A	US 20020006948 A1 (HALFBRODT ET AL), 17 January 2002 (17.01.2002), paragraph [0383], examples 143,160,244	1-13

[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search
23 November 2005

Date of mailing of the international search report
29-11-2005

Name and mailing address of the ISA/
Swedish Patent Office
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Eva Johansson/BS
Telephone No. +46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 2005/001399

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 2005021547 A2 (PHARMAXIS PTY LTD.), 10 March 2005 (10.03.2005)	1-13
	--	
A	HOLENZ JÖRG ET AL, "Medicinal Chemistry Driven Approaches Toward Novel and Selective Serotonin 5-HT6 Receptor Ligands", J.Med.Chem. 2005, Vol. 48, p. 1781-1795, table 1, compound 16, abstract	1-13
	--	

INTERNATIONAL SEARCH REPORT
Information on patent family members

29/10/2005

International application No.
PCT/SE 2005/001399

WO	2005030761	A1	07/04/2005	SE	0302570	D	00/00/0000
WO	2005030762	A1	07/04/2005	SE	0302572	D	00/00/0000
US	20040116465	A1	17/06/2004	AU	7477201	A	14/01/2002
				BG	108271	A	30/12/2004
				CA	2414995	A	10/01/2002
				CA	2444381	A	31/10/2002
				CN	1503787	A	09/06/2004
				CZ	20032833	A	12/05/2004
				EE	200300524	A	16/02/2004
				EP	1307481	A	07/05/2003
				EP	1390350	A	25/02/2004
				HU	0303825	A	01/03/2004
				IL	158142	D	00/00/0000
				JP	2004502416	T	29/01/2004
				JP	2004528334	T	16/09/2004
				MX	PA03009558	A	12/02/2004
				NO	20034665	A	10/12/2003
				NZ	528403	A	27/05/2005
				PL	366517	A	07/02/2005
				SE	0101387	D	00/00/0000
				SK	13032003	A	03/01/2005
				WO	02085866	A	31/10/2002
				ZA	200307752	A	03/01/2005
				SE	524944	C	26/10/2004
				SE	0200769	A	15/09/2003
US	20020006948	A1	17/01/2002	AU	782993	B	15/09/2005
				AU	4233201	A	24/07/2001
				BG	106821	A	31/01/2003
				BR	0107628	A	08/10/2002
				CA	2396227	A	19/07/2001
				CN	1395568	A,T	05/02/2003
				CZ	20022420	A	16/10/2002
				EE	200200390	A	15/10/2003
				EP	1246808	A	09/10/2002
				HR	20020664	A	30/04/2005
				HU	0204011	A	28/05/2003
				IL	150150	D	00/00/0000
				JP	2003523961	T	12/08/2003
				MX	PA02005742	A	18/09/2002
				NO	20023362	A	13/09/2002
				NZ	519326	A	25/02/2005
				PL	356091	A	14/06/2004
				SK	10002002	A	04/02/2003
				WO	0151473	A	19/07/2001
				ZA	200206470	A	19/02/2004
WO	2005021547	A2	10/03/2005	NONE			